Twenty-Third Annual Meeting
New York City, May 29-June 2, 1957

VOLUME XXXI NUMBER 1

DISEASES

of the

CHEST

OFFICIAL PUBLICATION

AMERICAN COLLEGE OF CHEST PHYSICIANS
René Laënnec

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Cohen, R. V.; Molthan, L., and Zarafonetis, C. J. D.: Clinical Studies of Various Forms of PAS (with special reference to plasma concentrations), *Diseases of the Chest* *30*:418-428 (Oct.) 1956.

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[1]Dr. Samuel Phillips: *Calcium Benzoyl PAS*, Paper presented at 15th VA-Army-Navy Conference on Chemotherapy of Tuberculosis, St. Louis, Missouri, February 6-9, 1956.

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*Miller, J.B., et al.: Ann. Allergy, 12:611, Sept.-Oct., 1954.

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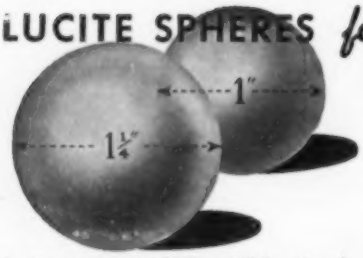

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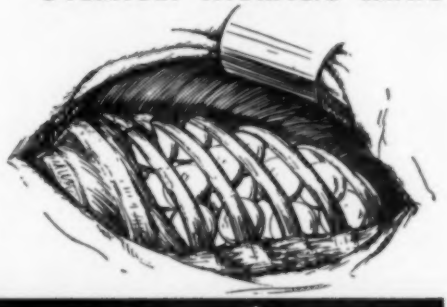

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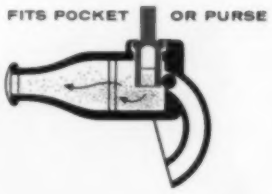

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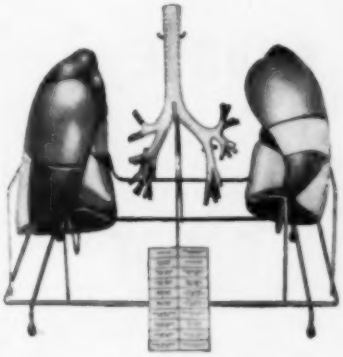

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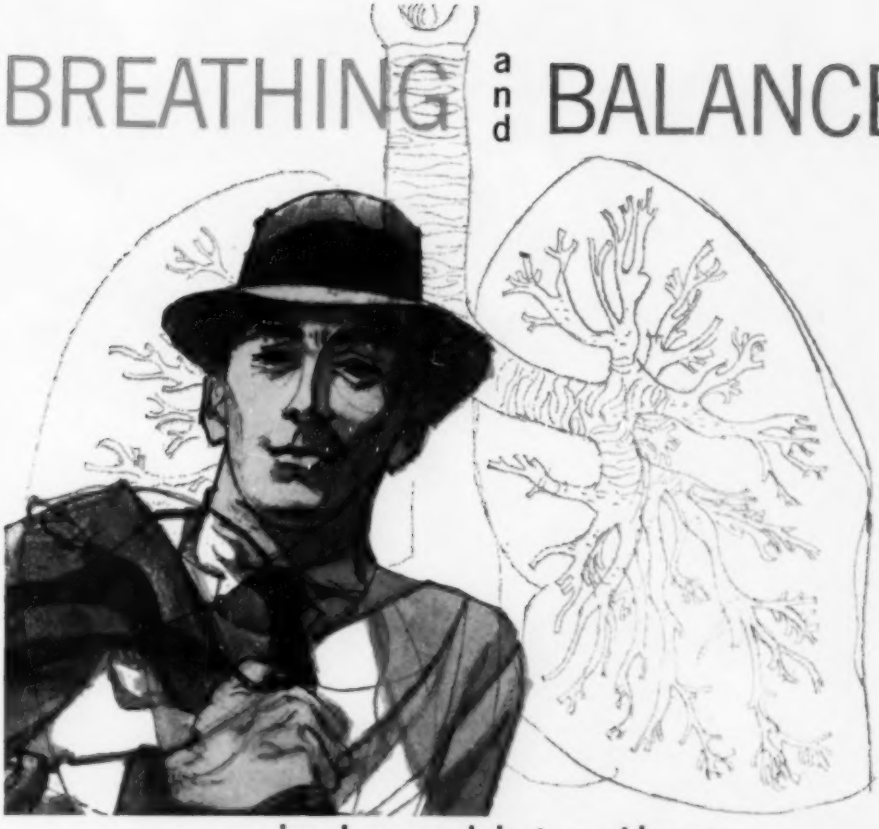

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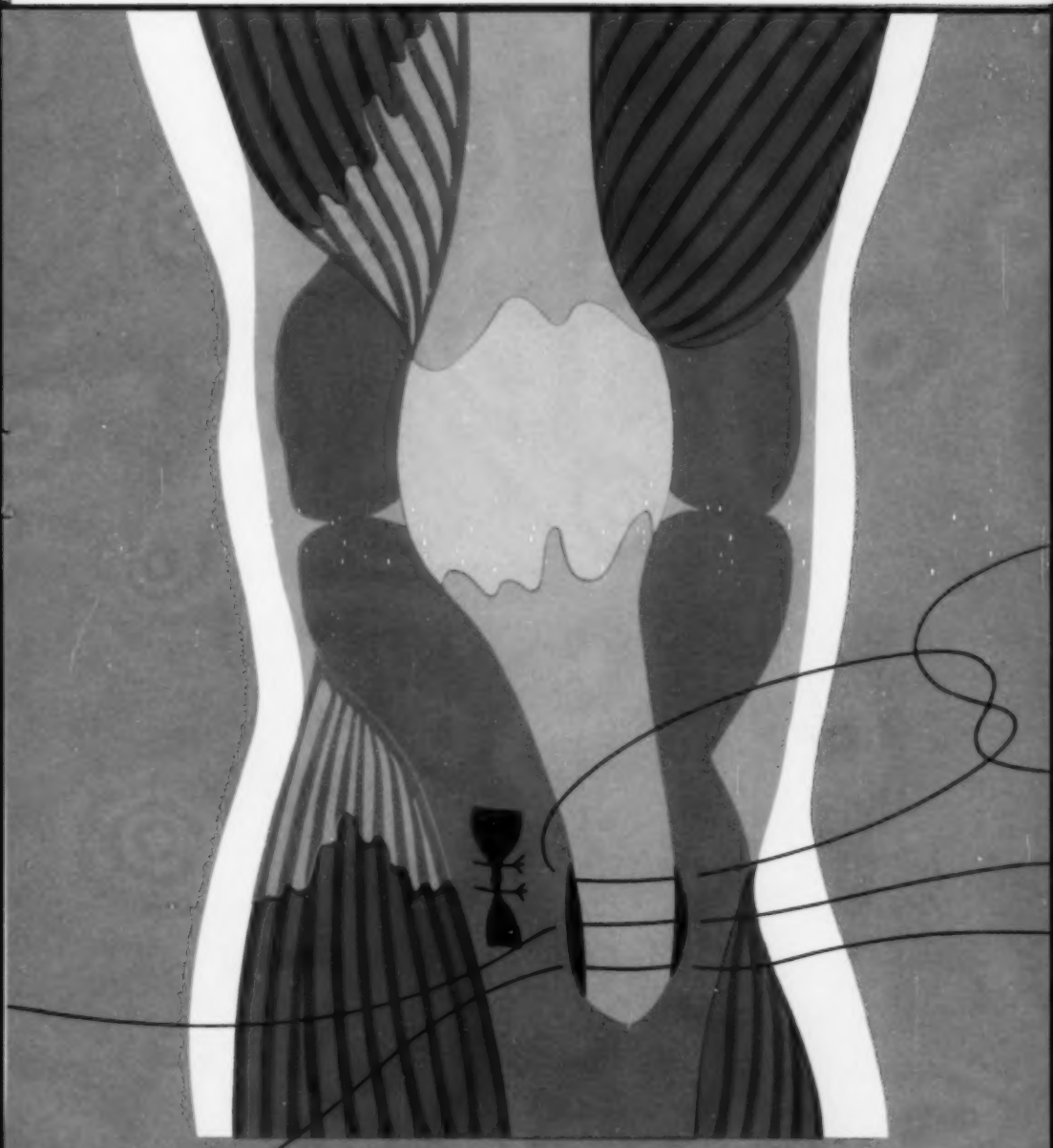

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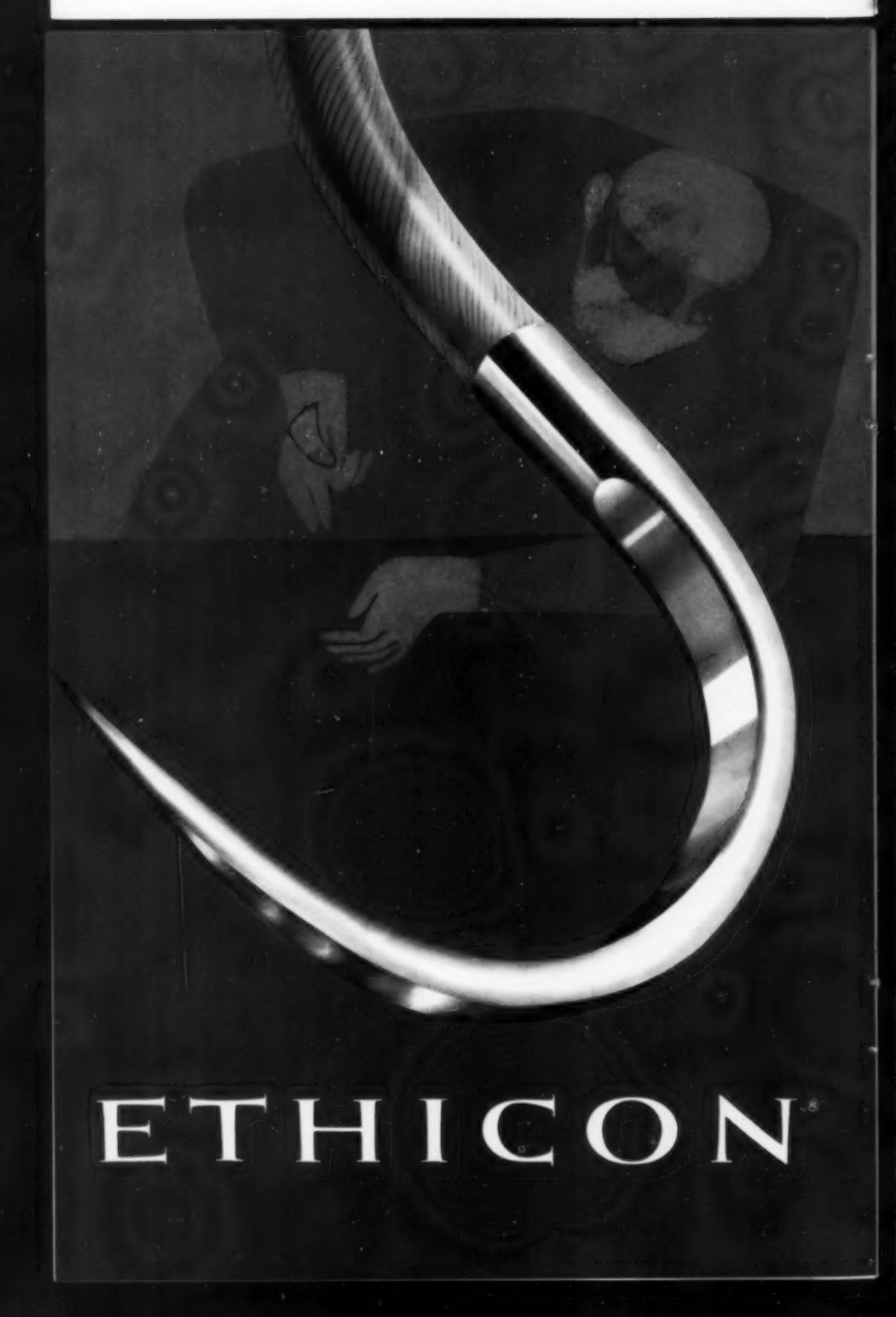
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1. Blanchard, K., and Ford, R. A.: Journal-Lancet 74:443, 1954.
2. Blanchard, K., and Ford R. A.: Rocky Mt. M. J. 52:278, 1955. 3. Cass, L. J., and Frederik, W. S.: Am. Pract. & Dig. Treat. 2:844, 1951.

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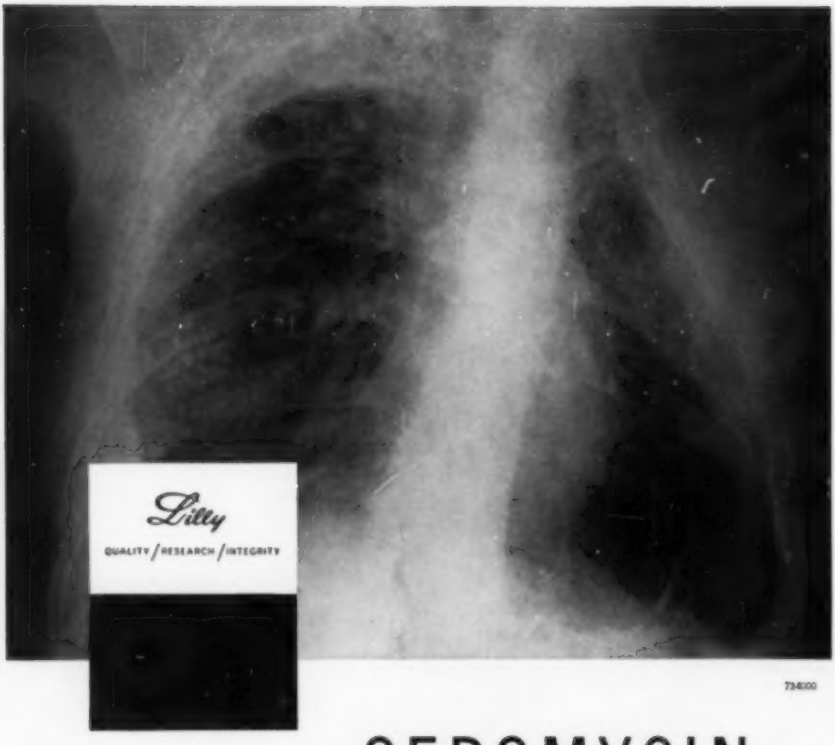

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DISEASES of the CHEST

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SEYMOUR M. FARBER, M.D., F.C.C.P., DAVID A. WOOD, M.D., SAMUEL L. PHARR, M.S., and BERNARD PIERSON, M.D.*

San Francisco, California

In a relatively new field of study, such as pulmonary cytology, one is impressed by rapid changes in diagnostic acumen and confidence which occur during the space of a few years. During our years of investigative research in sputum cytologic studies for the detection of malignant cells, we have attempted to correlate appearances of the stained cells with any available histologic, roentgenologic and clinical findings, and we have been particularly interested in reviewing those cases in which our laboratory has made a false "positive" or false "suspicious" report of cancer.

In the course of this investigation it has become apparent that cytologic appearances of the cells in a large number of non-malignant pulmonary conditions may be quite characteristic of the specific disease. Equally important, they may show close resemblance to carcinoma cells. This was found to be true for such widely different conditions as bronchial squamous metaplasia, pulmonary infarction, asthma, and lipid pneumonia. We feel that careful evaluation of these cellular alterations will serve two purposes. In the first place, since many of these pathologic states produce cells which cytologically closely resemble cancer cells, cognizance of their possible presence should assist in reducing to an absolute minimum the hazard of false positive reports. Secondly, we have found that identification of these cellular alterations can often contribute materially to a differential diagnosis in a number of non-neoplastic pulmonary diseases.

Cytologic Criteria for Malignancy

The most reliable criteria for establishing malignancy of cells found in the sputum, as well as in other body fluids, pertain strictly to the concept of exfoliative cytology and, therefore, are based upon nuclear features. This is not to minimize the significance of cellular grouping, but in our experience the majority of false "positive" and false "suspicious" (or "inconclusive") reports have resulted from undue emphasis being placed on

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the presence of cellular groupings, which to the unwary may suggest changes associated with cancer. While no single criterion can be relied upon by itself, we believe nuclear changes are much less likely to be erroneously interpreted.

Perhaps the most important single criterion for identification of malignant cells is increased nuclear size (Figure 1), with a corresponding increase in the nuclear-cytoplasmic ratio. Nuclear hyperchromatism also constitutes a strong presumptive evidence of malignancy, particularly when the chromatin is irregularly distributed and the nuclear rim is dense or "thick." Enlarged, multiple or jagged nucleoli are also of significance in leading to a diagnosis of malignancy, (Figure 2). Infrequently, nucleoli may be of such giant dimensions that the malignant nature of the cell is unquestionable.

The initial impression of malignancy in smears is usually suggested by the finding of single "suspicious" cells, and this impression is further strengthened when groups of such cells show relative variations in nuclear size, shape and structure as compared to normal cells. Accurate interpretation and evaluation, of course, is complicated by the fact that there is never a situation in which all the cells observed can be neatly separated into benign and malignant. Frequently, conclusively malignant cells are greatly outnumbered by atypical cells which, while not clearly malignant, offer supportive evidence of malignancy.

Cytologic Findings in Non-Malignant Disease

Production of sputum in sufficient quantity for cytologic study generally indicates the presence of some pulmonary abnormality. Therefore, the

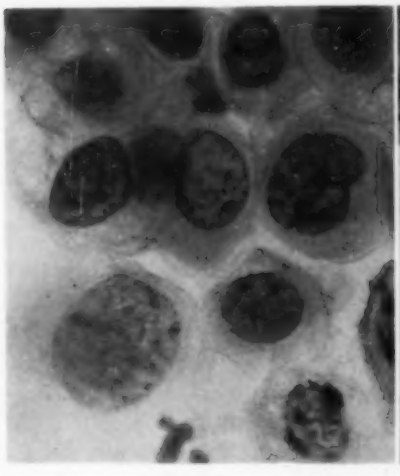

FIGURE 1

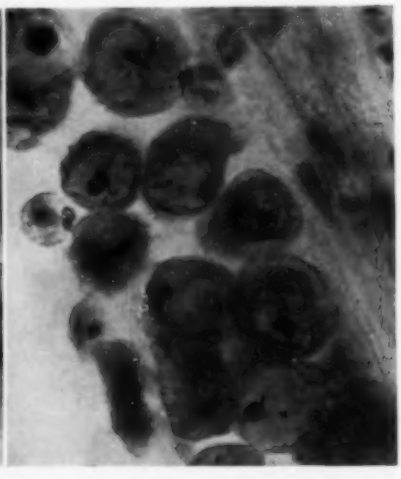

FIGURE 2

Figure 1: Malignant cells in sputum showing marked enlargement of nuclei and irregular distribution of chromatin. (× 760).—*Figure 2:* Malignant cells in sputum showing enlarged and multiple nucleoli. (× 760).

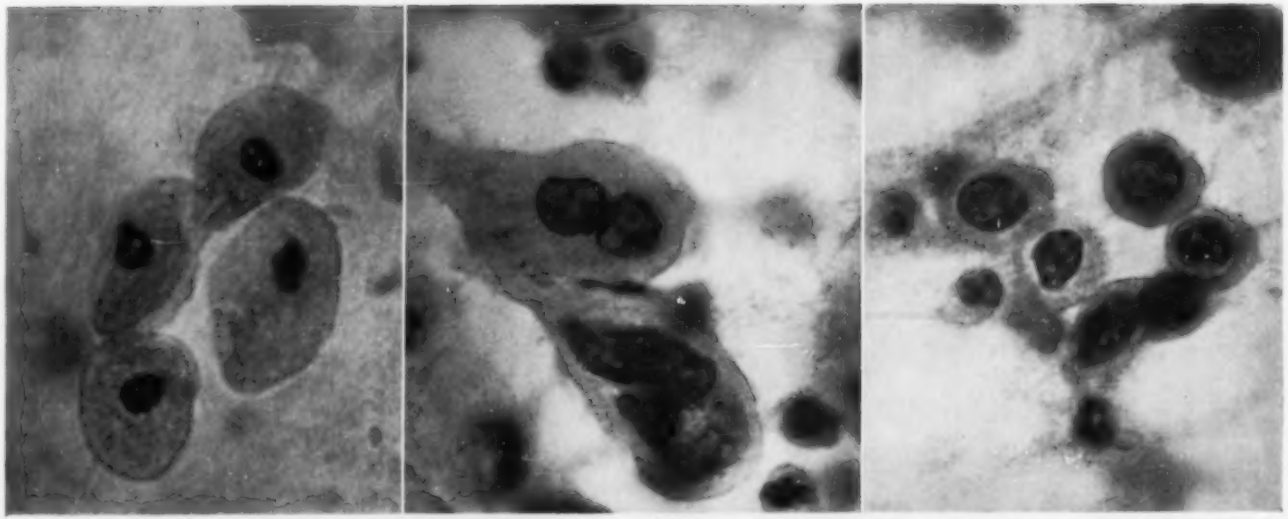

FIGURE 3 FIGURE 4 FIGURE 5

Figure 3: Stained sputum smear showing typical cells exfoliated from an area of bronchial metaplasia. (× 760).—*Figure 4:* Typical cells in sputum from a bronchogenic epidermoid carcinoma showing multiple, enlarged, hyperchromatic nuclei (× 760).—*Figure 5:* Bizarre metaplastic cells in sputum smear which are suggestive of epidermoid carcinoma, although nuclear criteria of malignancy are lacking. (× 760).

cells "normally" found in sputum smears are usually the consequence of a pathologic process, and in this sense differ from cells found in normal vaginal secretions and normal gastric washings. Thus, they usually exhibit some degree of cellular abnormality. In many cases such abnormal or altered cells may show features which possess a cursory resemblance to those of malignancy; or, as in the case of lipid pneumonia, coccidioidomycosis and other conditions, the cytologic findings may suggest the specific disease process. It must be stressed that (a) differentiation of abnormal from malignant cells is possible primarily through the application of rigid *nuclear* criteria. Further, it must be emphasized that a cytologic diagnosis of a non-malignant pulmonary disease, like that of malignancy, is equivocal and demands confirmation by appropriate clinical studies.

Bronchial Metaplasia: In any chronic pulmonary disease, portions of the tall columnar epithelium which normally line the bronchi may be replaced by areas of stratified squamous epithelium whose superficial cells may or may not be keratinized. This condition, metaplasia of the bronchial mucous membrane, constitutes one of the most common problems encountered in pulmonary cytologic studies. In our earlier work it was responsible for a substantial number of erroneous diagnoses of epidermoid carcinoma. In both conditions the cells are hyperkeratinized and stain a brilliant orange by the Papanicolaou method. Metaplastic cells as well as many of the epidermoid carcinoma cells are generally spherical or slightly flattened and contain a single, centrally placed nucleus. The metaplastic nucleus is typically pyknotic, in contrast to the enlarged, hyperchromatic

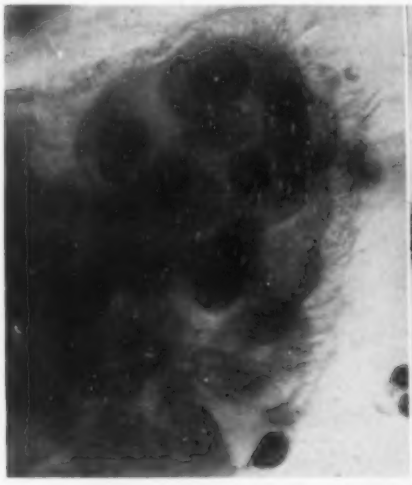

FIGURE 6

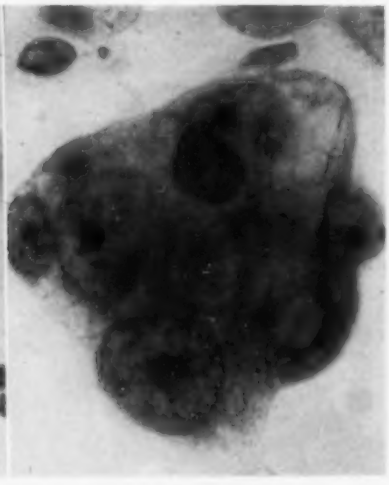

FIGURE 7

Figure 6: Tight, vacuolated cell groups sometimes seen in sputum from patients with bronchial asthma which may resemble acini of adenocarcinoma. Note cilia along periphery of group. (× 760).—*Figure 7:* Typical malignant acinus of adenocarcinoma seen in a stained sputum smear. Note prominent nucleoli and variation in nuclear size and a chromatin distribution. (× 760).

nucleus characteristic of epidermoid carcinoma. Thus, typical metaplastic cells (Figure 3) are readily distinguished from the typical malignant cells (Figure 4) of epidermoid carcinoma. This simplicity is complicated, however, by the fact that bizarre forms frequently are found in both conditions, so that cells are often encountered which are neither definitely metaplastic nor conclusively malignant (Figure 5). This situation of bizarre metaplasia emphasizes again the need to employ rigid *nuclear* criteria in order to eliminate as far as possible in suspected cases of epidermoid carcinoma cytologic error.

FIG. 8A

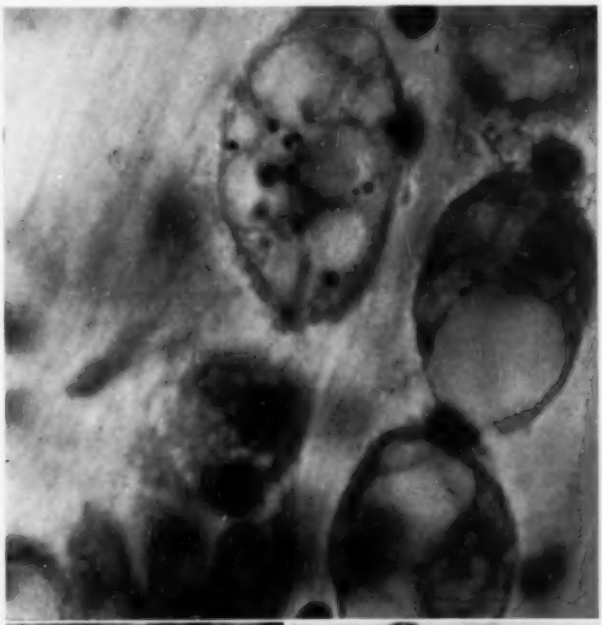

FIG. 8B

FIG. 8C

Figure 8, A, B and C: Characteristic pulmonary macrophages showing the empty, "Swiss cheese" vacuolation seen in cases of lipid pneumonia. (× 760).

Interestingly, sputum smears which show cells unequivocally of epidermoid carcinoma consistently contain numerous supporting "metaplastic" cells which may range from typical through bizarre to frankly suspicious forms. In view of the uncertainty of our knowledge concerning the role of metaplasia in carcinogenesis, this problem of cytologic differentiation is not surprising.

Asthma and Allergy: In our early work in pulmonary cytology, sputum from a number of patients with bronchial asthma was reported to contain malignant cells. In retrospect, when follow-up studies demonstrated that no malignancy was present, the smears were carefully re-evaluated. It was found that error had resulted from interpretation of tight, highly vacuolated groups of cells which are commonly present in the sputa of asthmatic patients (Figure 6) and confusing them with those which occur in the acini grouping of adenocarcinoma (Figure 7). Closer inspection showed that although both groups are somewhat similar in histioid cellular arrangement, the nuclei of the cells associated with asthma are uniformly small and show none of the nuclear features of malignancy. In addition, cilia are frequently seen along the periphery of benign cell groups. The associated findings of Curschmann spirals and eosinophiles in the sputum is further evidence that this is a benign atypia. However, since Curschmann spirals and eosinophiles are also frequently found in the sputum in cases of malignancy, careful evaluation of nuclear morphology as well as a search for ciliated cells within the groups are required for definitive identification.

Lipid pneumonia: Since organized lipid pneumonia may simulate neo-

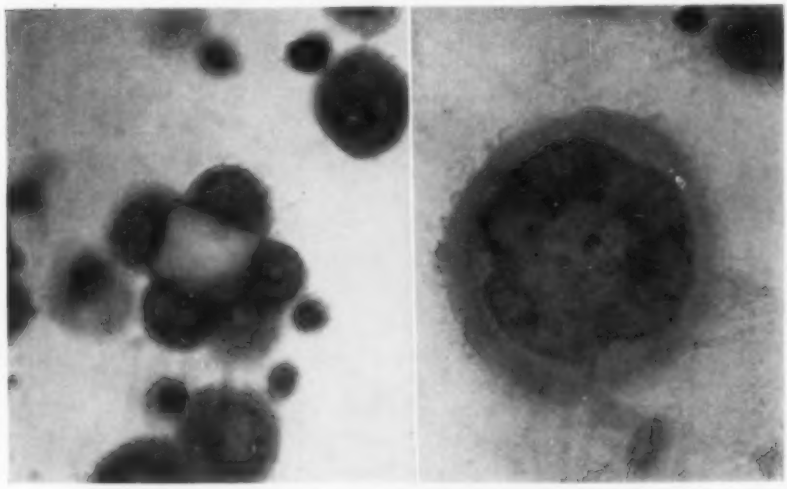

FIGURE 9 FIGURE 10

Figure 9: Mesothelial "rosette" in non-malignant pleural effusion. (× 760).—*Figure 10:* Mesothelial cell showing the tremendous nuclear enlargement which may be seen in cells of the pleural fluid from cases of pulmonary infarction. Compare with normal mesothelial cells, at the same magnification, in Figure 9. (× 760).

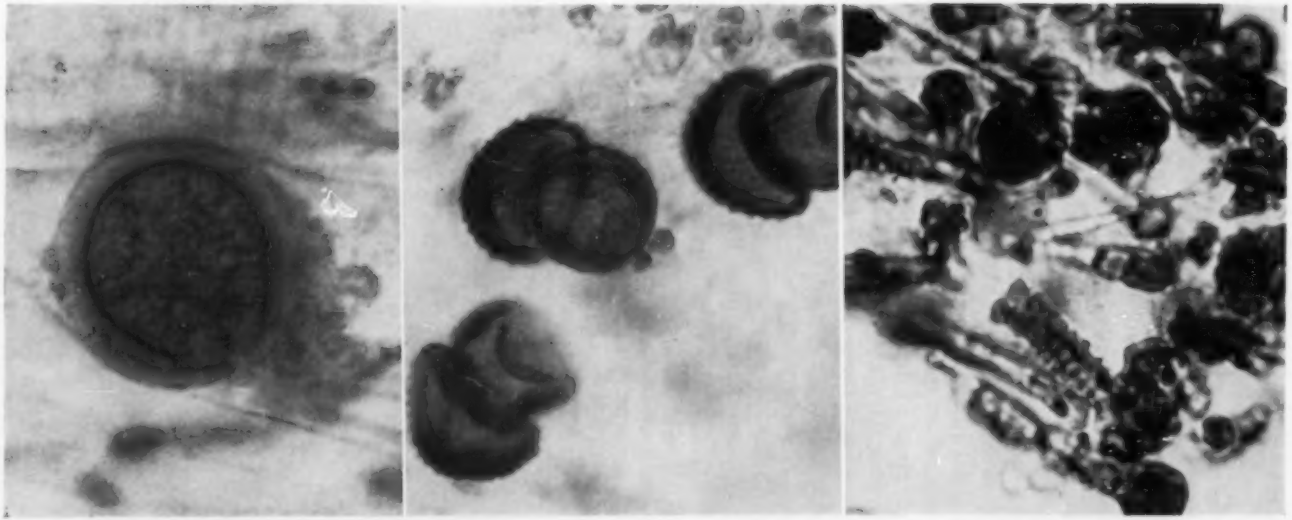

FIGURE 11 FIGURE 12 FIGURE 13

Figure 11: Coccidioides seen in stained sputum smear. Note distinct endospores. (× 760).—*Figure 12:* Stained sputum smear showing pollen bodies which may resemble coccidioides. Note that they are hemispherical and contain an amorphous central material, in contrast to the distinct endospores of Figure 11. (× 760).—*Figure 13:* Lung section showing intra-alveolar collection of asbestos bodies. (× 760).

plasm both clinically and roentgenologically, we have occasionally been called upon to study the sputum of patients who were later shown to have had this disease. In some of the cases a diagnosis of lipid pneumonia had been suggested by the presence in the stained smears (Figure 8) of characteristic hypervacuolated macrophages and histiocytic syncitia. These enlarged cells of reticulo-endothelial origin contain tremendous, spherical and seemingly empty vacuoles within their cytoplasm which produce a "Swiss cheese" appearance. Normally, although histiocytic cells show vacuolations, the normal vacuoles are much smaller and interlace with one another, conferring a spongy appearance to the cytoplasm.

Frequently, lipid pneumonia may be overlooked in differential diagnosis because of its widely variable manifestations. It may follow aspiration of an oily substance in nasal sprays. It occurs perhaps as frequently in adults with no history of aspiration but who habitually take mineral oil or oily nose drops before retiring. In debilitated children it may also follow the use of cod liver oil. During sleep, the oil which coats the oral and pharyngeal mucosa may drain slowly into the bronchial tree. Progressive accumulation of this non-absorbable substance over a period of time finally results in foreign body reaction, secondary infection and extensive fibrosis. A pronounced reticuloendothelial response ensues as macrophages attempt to phagocytize and remove the foreign lipid material. It is the presence of these hypervacuolated cells in stained sputum smears which points to the diagnosis of lipid pneumonia. The lipid is removed from the cells in the process of alcoholic fixation and staining; however, the characteristic morphologic appearance remains. Further study of specimens specifically stained to demonstrate intracellular fat will aid in definitive diagnosis.

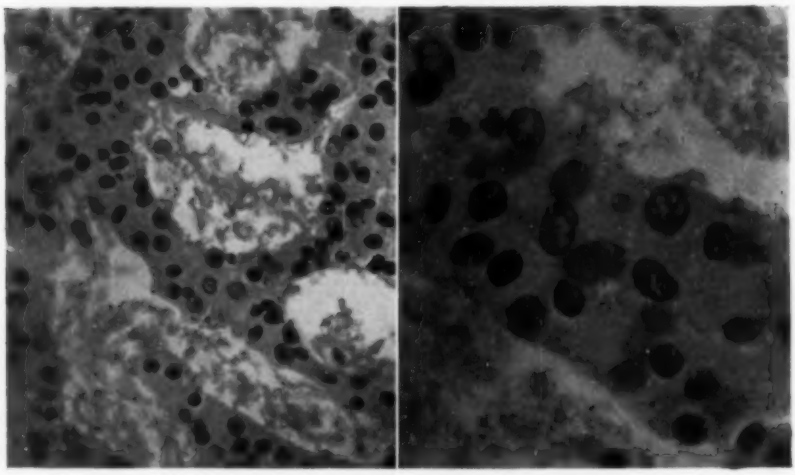

FIGURE 14A FIGURE 14B

Figure 14A: Cytologic preparation made at bronchoscopy showing cords of cells aspirated from a bronchial adenoma. (× 480).—*Figure 14B:* Higher magnification of cells from a bronchial adenoma. (× 760).

Incidentally, since sputum in cases of lipid pneumonia may contain free oily material, it may be difficult to make the specimen adhere to the glass slide. This gross finding alone may suggest the possibility of lipid pneumonia.

Pulmonary infarction: Abnormal cells in the sputum may result from pulmonary infarction, although in our experience this is rare. Extremely bizarre mesothelial cells may, however, predominate in cytologic smears of the pleural fluid sediments from pulmonary infarction cases. Many of the morphologic changes which are generally associated with malignant cells may be exhibited by these cells. This finding has been reported by others.[4] We believe this cytologic finding may be transitory, occurring as an initial reaction of pleural mesothelium to infarction of the lung. This observation is based upon the disappearance of abnormal cells in subsequent studies from patients who initially showed the reaction.

We have observed these cells to occur singly in the smears, although occasionally, small clusters of rosette formations of abnormal cells have been seen. Such grouping lacks the tight formation and smooth periphery which is seen in true acini of adenocarcinoma. Some groups, as well as single cells, contain cytoplasmic vacuolization; however, these do not include the extremely large ones which are associated with malignant cells. The nuclei of "infarction cells" are markedly enlarged and contain a fine distribution of chromatin. Occasionally smaller nuclei are seen with condensation of chromatin resulting in nuclear pyknosis, but not hyperchromatism. The nuclear membrane is relatively thin and the nuclear contour reveals a scalloped irregularity, but is seldom jagged. The nucleoli of "infarction cells" closely resemble those of malignant nuclei and are multiple (usually three or more), enlarged and irregular. Mitotic cells may be abundant in cases of pulmonary infarction.

The strong possibility of cytologic error in cases of pulmonary infarction has increased our conviction that demonstration of both *nuclear* features of malignancy and grouping consistent with malignancy are needed to justify a positive cytologic report for pleural fluid sediment. It is essential to obtain pertinent clinical information when examining pleural fluid sediments for the detection of malignant cells. A more complete investigation of this source of cytologic error is needed in a series of clinically known cases of pulmonary infarction, obtained during the acute and healing phases of this condition.

Coccidioidomycosis: Although this fungus disease is endemic in southwestern United States, and particularly in central and southern California, it occurs sporadically in other sections of the country. Two forms of the disease are seen: a relatively benign disease of short duration which may simulate pneumonia, and a prolonged process, usually granulomatous, which may produce multiple pulmonary lesions almost from the beginning. The latter form is apt to suggest lung cancer, particularly metastatic tumor, and we have been called upon to study a few of these cases. The presence of spherules containing endospores (Figure 11) in the stained sputum has

led to the diagnosis of coccidioidomycosis in several of these cases. In vivo, the fungus, *Coccidioides immitis,* multiplies by endosporulation and characteristically is productive of refractile, double-walled spherules which range from 10 to 300 micra in diameter. In the larger forms, well-defined endospores may be recognized, thus permitting cytologic identification of the fungus.

Some care must be exercised to distinguish the spores of coccidioidomycosis from contaminants, especially pollen (Figure 12). Pollen bodies are generally hemispherical, rather than spherical, and may contain round granules which resemble, but are less distinct than, the well-defined endospores of *Coccidioides.* In addition, pollen bodies usually manifest a central stellate nucleus, whereas Coccidioides has no nucleus. Pollen bodies may represent air-borne contamination of the specimen, or they may have reached the bronchial tract by inhalation.

Although cytologic demonstration of spores has not been consistently accomplished in cases of known coccidioidomycosis, the possibility of this disease should be kept in mind during cytologic studies, particularly when the patient is known to have lived in an endemic area. Definitive diagnosis, of course, should be established by sputum cultures and serum antibody studies.

Pneumoconiosis: We have been unable, so far, to associate specific cytologic findings with pneumoconiosis. Perhaps the only consistent finding we have observed has been the abundance of macrophages filled with amorphous and particulate material. We have been unable either to identify the specific inclusions, or to distinguish them from the intracellular inclusions of carbon which are "normally" present in pulmonary macrophages. One might expect to identify asbestos bodies (Figure 13) in cases of asbestosis. Although we rarely see this disease in the San Francisco area, we anticipate such cases as we may have the opportunity to study.

Bronchial adenoma: If pathologic studies were any guide, this abnormality ought to be readily identified cytologically since the cellular structure is usually remarkably uniform and the cells show an ample nuclear-cytoplasmic ratio. However, since these tumors are separated from the bronchial surface either by normal bronchial mucosa or by an arcade of squamous metaplasia, one would not expect ordinarily to find exfoliated tumor cells in specimens of bronchial secretions. One of us (BP), however, recently studied a case in which numerous typical cells from a bronchial adenoma were found in smears prepared from bronchial aspiration obtained during bronchoscopy. In our experience and knowledge this is the first reported case in which correct cytologic diagnosis of this entity was made. In its study, only the first and second of three bronchial aspirations resulted in the cytologic findings of tumor cells. It is assumed that this was possible because the fragile and congested mucosa was traumatized by the bronchoscopy with the result that tumor cells were detached into the aspirated material. The cells were found singly, as well as in fairly large groups arranged in cords and trabeculae (Figure 14). The cuboidal cells had poorly defined cytoplasmic borders and the nuclei were uniformly

round, ranging from 10-15 micra in diameter (Figure 15). Although we feel that this is an interesting cytologic observation, we emphasize that success in applying cytologic methods to the detection of bronchial adenomas is unlikely, since the epithelium overlying the tumor is usually intact and prevents the exfoliation of tumor cells into the bronchial lumen.

SUMMARY

While the cytologic examination of sputum, in the hands of experienced pathologists and their co-workers, can be an accurate and useful method, it must be pointed out that the morphologic identification of cells is often difficult. This problem is more frequently associated with examination of sputum than cytologic examination of other body secretions, since sputum, in sufficient volume for study, generally indicates some type of pulmonary disease and consequent alteration of morphology.

Although the cellular changes observed in most non-malignant pulmonary diseases are minimal, some non-malignant pulmonary diseases produce cellular alterations which closely resemble those of malignancy, while still others result in cytologic findings indicative of a specific disease. Among the chest diseases and pathologic entities in the latter category are asthma, pulmonary infarction, lipid pneumonia, bronchial metaplasia, pneumoconiosis, coccidioidomycosis and bronchial adenoma.

It is hoped that greater attention to the cytologic findings in sputum smears from non-malignant pulmonary diseases will add ultimately a new dimension to the usefulness of exfoliative cytology. Acquaintance with the cytologic patterns attendant thereto should contribute materially to improvement in accuracy of diagnosis by providing a better basis of distinction between malignant cells and benign cellular abnormalities. In addition, the result of such a comparative study is of equal value as an aid toward definitive diagnosis of a number of non-malignant pulmonary diseases which clinically may be confused with cancer. The significance of employing rigid *nuclear* criteria for identifying malignant cells is emphasized, since similarities in cellular *grouping* rather than in *nuclear* features are the most common source of cytologic error.

RESUMEN

Si bien el examen citológico del esputo en manos de anatomopatólogos experimentados y de sus colaboradores puede ser un método precise y útil, debe señalarse qué identificación morfológica de las celdillas es a menudo difícil. Este problema es más frecuente cuando se examinan los esputos que cuando se trata de otras secreciones puesto que el esputo en suficiente volumen para su estudio generalmente indica alguna enfermedad pulmonar y ya hay en él la consecuente alteración de la morfología.

Aunque los cambios celulares observados en la mayoría de las enfermedades pulmonares no malignas son mínimos, algunas enfermedades no malignas producen alteraciones celulares que se parecen mucho a las de la malignidad y hay otras que indican una enfermedad específica. Entre las afecciones torácicas de la última categoría se encuentran el asma, el infarto pulmonar, neumonía lipoidica, metaplasia bronquial, neumoconiosis, cocci-

dioidomicosis y el adenoma bronquial.

Es de esperarse que una mayor atención a los hallazgos citológicos en los esputos de afecciones pulmonares no malignas, termine por agregar un campo nuevo en la utilización de citología exfoliativa.

El conocer los aspectos citológicos hasta aquí asentados, contribuirá materialmente a mejorar la exactitud del diagnóstico al proveer una base más segura en el diagnóstico diferencial entre las células malignas y no malignas. Además, el resultado de tal estudio comparativo es de igual valor como un auxiliar que lleve al diagnóstico definitivo de ciertas enfermedades no malignas que pueden confundirse con el cáncer. La significación de usar un criterio rígido *nuclear* para identificar las células se recalca, puesto que las similaridades del *agrupamiento* celular más que las características *nucleares* son la fuente de error citológico común.

RESUME

Bien que l'examen cytologique de l'expectoration, entre les mains d'anatomo-pathologistes expérimentés et de leurs collaborateurs puisse être une méthode précise et efficace, on doit insister sur le fait que l'identification des cellules est souvent difficile. Ce problème est beaucoup plus le fait de l'expectoration des autres sécrétions. En effet, l'expectoration en volume suffisant pour être l'objet d'examen suppose déjà à elle seule une atteinte pathologique des poumons qui est susceptible d'entrainer des altérations morphologiques des cellules.

Bien que les altérations cellulaires observées dans la plupart des affections pulmonaires non-malignes soient discrètes, certaines de ces affections peuvent entrainer des aspects qui ressemblent de près au cancer, tandis que d'autres permettent d'avoir la preuve cytologique d'une affection spécifique. Parmi les affections du thorax de cette catégorie, figurent l'asthme, l'infarctus pulmonaire, la pneumonie lipoïdique, la métaplasie bronchique, la pneumoconiose, la coccidioidomycose et l'adénome bronchique.

Les auteurs espèrent qu'une plus grande attention accordée aux constatations cytologiques dans les frottis d'expectoration provenant d'affections pulmonaires non-malignes permettra ultérieurement d'augmenter la valeur de la cytologie. En perfectionnant nos connaissances des aspects cytologiques, on devrait arriver à faciliter le diagnostic grâce à une meilleure discrimination entre cellules malignes et anomalies bénignes. De plus, le résultat d'une telle étude comporte un autre intérêt: c'est de permettre un diagnostic précis de certaines affections pulmonaires non-malignes, qui peuvent être cliniquement confondues avec le cancer. Les auteurs insistent sur l'importance d'utiliser des critères irréfutables de l'aspect du noyau pour identifier les cellules malignes. Ce sont en effet plus les similitudes du groupement cellulaire que les caractéristiques nucléaires qui sont le plus souvent à l'origine des erreurs de diagnostic cytologique.

ZUSAMMENFASSUNG

Während die cytologische Untersuchung von Sputum in den Händen erfahrener Pathologen und ihrer Mitarbeiter eine genaue und nützliche

Methode sein kann, muss darauf hingewiesen werden, dass die morphologische Identifizierung von Zellen oft schwierig ist. Dieses Problem tritt häufiger auf in Verbindung mit der Auswurfuntersuchung als die cytologische Untersuchung anderer Körperausscheidungen, weil der Auswurf in genügender Menge für die Untersuchung im allgemeinen irgendwelche Formen von Lungenkrankheit anzeigt und eine entsprechende Abwandlung der Morphologie.

Obwohl die zellulären Veränderungen, die bei den meist nicht bösartigen Lungenkrankheiten beobachtet werden, minimal sind, führen einige nicht bösartige Lungenkrankheiten zu zellulären Abwandlungen, sehr ähnlich denen bei bösartigkeit, während wieder andere cytologische Befunde zur Folge haben, die eine spezifische Krankheit anzeigen. Unter den Thoraxkrankheiten und pathologischen Einheiten der letztgenannten Kategorie befinden sich Asthma, Lungeninfarkt, Lipoid-Pneumonie, bronchiale Metaplasie, Pneumonoconiose, Coccidioidomycose und Bronchial-Adenom.

Es ist zu hoffen, dass grössere Aufmerksamkeit auf die cytologischen Befunde bei Sputumausstrichen von nicht bösartigen Lungenkrankheiten der Brauchbarkeit der Cytologie abgestossener Zellen schliesslich ein neues Gebiet hinzufügen wird. Vertrautheit mit den damit zusammenhängenden cytologischen Strukturen muss wesentlich zur Verbesserung in der Genauigkeit der Diagnose beitragen, da sie eine besser Grundlage schafft für die Unterscheidung zwischen bösartigen Zellen und gutartigen zellulären Abnormalitäten. Zusätzlich ist das Ergebnis einer solchen vergleichenden Untersuchung von gleichem Wert, als eine Hilfe hinsichtlich einer definitiven Diagnose einer Anzahl von nicht bösartigen Lungenkrankheiten, die klinisch mit Krebs verwechselt werden können. Die Bedeutung der Verwendung eines strengen, auf den *Kern* bezogenen Kriteriums zur Identifizierung maligner Zellen wird betont, weil Ähnlichkeiten in der zellulären *Gruppen*bestimmung öfter als in den *Kern*strukturen die häufigste Quelle cytologischer Fehler sind.

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Acute Alterations of the Electrocardiogram Following Thoracic Surgery

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While occurrence of disturbances of cardiac rhythm during and after general surgical procedures has been known for many years[2, 11] interest in the subject was revived only recently with the advent of thoracic and in particular cardiac surgery. A number of reports dealing with postoperative changes of the electrocardiogram have appeared, mostly after pulmonary resection.[1, 3, 6, 13, 15] Various arrhythmias have been noted postoperatively often associated with transient surgical pericarditis and diverse factors have been implicated in their development.[3, 6, 7, 9, 17]

In the course of our own observations we have been impressed by the high incidence of arrhythmias developing in patients undergoing surgery for carcinoma of the esophagus, a point previously not stressed. Furthermore, a characteristic electrocardiographic pattern was found consistently in our patients who developed surgical pericarditis after mitral commissurotomy. These two features as well as the incidence and analysis of the causes of disturbances of rhythm in our entire patient material submitted to thoracic and cardiac surgery are the subject of the present report. Changes in electrocardiographic contour attributable to the surgical trauma of the heart itself and to hemodynamic alterations following surgical procedures for the correction of congenital heart disease are at present under study.

Material and Methods

Clinical records and the electrocardiograms of 135 patients who underwent various types of thoracic or cardiac surgery at Michael Reese Hospital have been reviewed. Of these, 66 had at least one postoperative electrocardiogram. In 55 (Table I) the presence of sinus rhythm before surgery had been established on clinical and/or electrocardiographic grounds. There were 34 females and 32 males in this group. The ages ranged from six months to 78 years (Table III). Our material was classified as to the time of appearance of arrhythmias (Table IV), development of pericarditis (Table II) or a combination of both. The incidence of these alterations was related to the type of surgery performed (Tables I and II) and to the ultimate prognosis of these patients (Table III). Excluded from this study were those with simple postoperative sinus tachycardia or with occasional premature systoles appearing after surgery. No case of ventricular paroxysmal tachycardia was encountered.

From the Cardiovascular Department, Medical Research Institute, Michael Reese Hospital.

Aided by grants from the Hibse Research Fund and the Michael Reese Research Foundation.

Results

Disturbances of rhythm developed in 20 instances (Table I). Electrocardiographic evidence of pericarditis was found in 27 and questionable changes in three (Table II). Both arrhythmia and pericarditis occurred in 10 who had sinus rhythm prior to operation. There was a definitely higher incidence of arrhythmias in the older age group (Table III). Auricular flutter or fibrillation were the most common arrhythmias encountered (75 per cent) regardless of type of surgery and was the only disturbance of rhythm occurring following mitral commissurotomy. It developed in seven of the 13 patients in this latter group who had sinus rhythm prior to surgery. Paroxysmal auricular fibrillation and auricular premature systoles also developed in two in whom the pericardium was opened in the course of left pneumonectomy. In each of these instances arrhythmia was detected simultaneously with or after the onset of surgical pericarditis. On the other hand none of the four submitted to pulmonary valvulotomy developed an arrhythmia. Among the 10 patients who underwent surgery for carcinoma of the esophagus (esophagectomy with or without gastrectomy and one instance of exploratory thoracotomy), disturbances of rhythm were noted in seven—all of whom died within one to 22 days (Table III).

Most of the disturbances of rhythm occurred within five days after

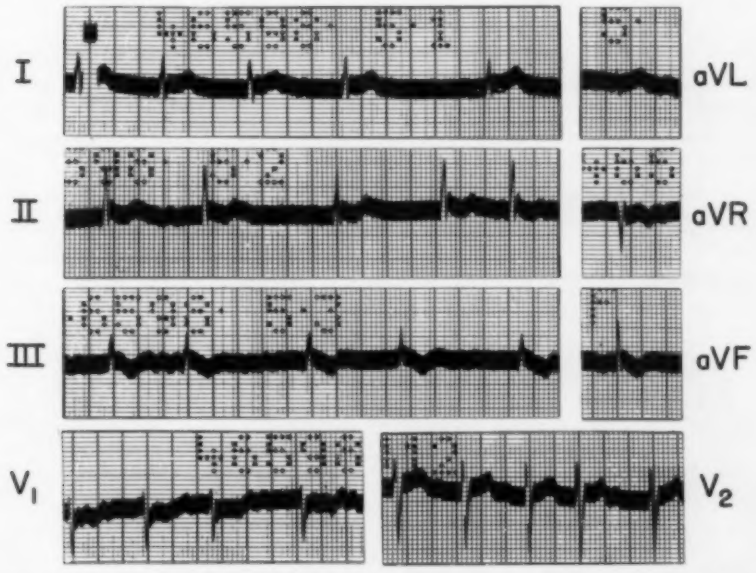

FIGURE 1: *A typical postoperative electrocardiogram* in a 42 year old fully digitalized patient, four days *after mitral commissurotomy* (only the two chest leads shown could be recorded because of bandages on chest.) Auricular fibrillation is present. Note the elevated S-T junction in leads II, III, aVF and V_2, the downward sloping S-T segment and the short Q-T interval, a combination considered characteristic for a pericarditis pattern modified by digitalis effect (cf. Figure 2).

operation (Table IV). In three instances the onset was delayed more than 10 days and in one auricular fibrillation appeared 24 days after mitral commissurotomy. In this last patient first and second degree A-V block developed at first during the immediate postoperative period, the only instance of disturbance of A-V conduction observed in our series. Reactivation of the rheumatic process was considered to have occurred in this patient. In the other three, a late arrhythmia developed in the course of grave postoperative complications, viz., tuberculous bronchopneumonia, pulmonary infarction and sero-fibrinous or fibrino-purulent pericarditis,

TABLE I

INCIDENCE OF ARRHYTHMIAS IN RELATION TO THE SURGICAL PROCEDURE IN PATIENTS WITH PREOPERATIVE SINUS RHYTHM

Operation	Total Number of Cases	Cases Developing					
		Auricular Flutter or Fibrillation	Auricular Premature Systoles	Supraventricular Paroxysmal Tachycardia	Nodal Premature Systoles	Nodal Paroxysmal Tachycardia	A-V Block
Mitral commissurotomy	13	7	....	....	....	....	1
Esophagectomy with or without gastrectomy	9	4	....	1	....	1	....
Exploratory thoracotomy (for carcinoma of esophagus)	1	....	....	....	1	....	....
*Thoracotomy (left) (for repair of spontaneous perforation of esophagus)	1	....	....	....	....	....	....
*Thoracotomy (left) (for empyema)	1	....	....	....	....	....	....
Pneumonectomy (right)	2	1	....	....	....	....	....
Pneumonectomy (left)	4	2	1	....	....	....	....
Lobectomy	4	1	....	....	....	....	....
Thoracoplasty	1	....	....	....	....	....	....
Pericardiotomy	1	....	....	1	....	....	....
Pericardiectomy	2	....	....	....	....	....	....
Dusting of pericardium	3	....	....	....	....	....	....
Decortication (right lung)	1	....	....	....	....	....	....
Patent ductus arteriosus	9	....	....	....	....	....	....
Pulmonary valvotomy	4	....	....	....	....	....	....
TOTAL	55	15	1	2	1	1	1
				20			

*Same patient.

the latter as the consequence of a fistula between a esophago-gastrostomy and the pericardial sac.

The pericardium was opened in the course of the operation, on purpose or inadvertently in 33 patients (Table II). Twenty-six (78.7 per cent) developed definite electrocardiographic evidence of pericarditis. In addition there was one instance with electrocardiographic changes suggestive of pericarditis after right pneumonectomy though pericardiotomy was not performed. Necropsy findings in five who underwent mitral commissurotomy and died in the immediate postoperative period (one of them not included in the present study because of the absence of postoperative electrocardiograms) have shown the presence of fibrinous pericarditis in every instance. In two, no electrocardiographic alterations of pericarditis were found even though a pericardial friction rub was detected clinically in both.

The electrocardiographic alterations caused by surgical pericarditis consisted in the usual S-T deviations found in other types of acute pericarditis with the usual evolution over three to four weeks. In several instances however the electrocardiogram returned quickly, within one or two weeks, to the preoperative pattern without going through intermediate stages of T flattening and inversion. Tracings recorded in early pericarditis after mitral commissurotomy revealed a strikingly similar and characteristic appearance (Figures 1 and 2) attributable to the modification of the ordinary pericarditis pattern by the concommitant digitalis therapy.

Discussion

Postoperative arrhythmias. The causes of disturbances of cardiac rhythm following surgical procedures have been studied experimentally and analyzed clinically. It would appear that age plays a role in their development since arrhythmias seldom occur when thoracic surgery is performed in patients under 40 years of age,[5, 13] in particular auricular fibrillation. However, coronary disease seems to bear no direct relationship to its incidence.[4] In our 20 patients who developed a postoperative arrhythmia, evidence of coronary involvement was present only in two.

Experimental data suggest that hypoxemia may be responsible for

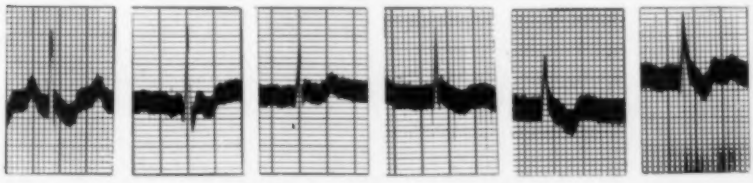

FIGURE 2: Lead II in *six different digitalized patients* two to six days *after mitral commissurotomy* showing the three kinds of electrocardiographic findings. Auricular fibrillation was present in all except the first. In all the S-T junction is elevated, S-T forms a downward slope and merges with a diphasic or upright T wave while Q-T appears fore-shortened. In the first four cases S-T starts from an S wave, and in the middle two the latter is pulled above its reference level; in the last two cases the elevated S-T merges with a terminal notching of QRS, an quivalent of an S wave. These three types of electrocardiographic alterations are attributable to the combined effects of an acute pericarditis and of digitalis.

development of some types of cardiac arrhythmias,[10, 19, 20] and this has to be considered especially in cases of total pneumonectomy. Bailey and Betts[1] noted a relationship between the varying extent of pneumonectomy and the incidence of disturbances of cardiac rhythm. Among our four patients who underwent resection of a single lobe auricular fibrillation occurred in only one, a 51 year old female with tuberculosis. Prior to its onset post-operative complications developed including pneumothorax with collapse of the remaining lobes of the operated lung.

It is well known that vagal stimulation facilitates the experimental production of auricular flutter and fibrillation.[12, 16, 18, 20] Vagal stimulation during infection of the bronchial stump has been implicated as a cause of occurrence of this arrhythmia after pneumonectomy.[1] But vagal irritation can be expected to occur in any type of intrathoracic surgical procedure and need not necessarily be related to this particular event. That this is so is

TABLE II

ELECTROCARDIOGRAPHIC EVIDENCE OF PERICARDITIS IN RELATION TO THE TYPE OF SURGICAL PROCEDURE

Operation	Total Number of Cases	Number with Pericardium Opened	Number with Definite ECG Evidence	Number with Questionable ECG Evidence
Mitral commissurotomy	24	24	18	2
Pulmonary valvotomy	4	4	3	1
Dusting of pericardium	3	3	3	0
Pneumonectomy	3	2	3	0
TOTAL	34	33	27	3

TABLE III

POSTOPERATIVE ARRHYTHMIAS IN RELATION TO AGE AND OUTCOME*

Age in Years	Total Number of Cases	Arrhythmia	Per Cent	Deaths
0 - 10	7	0	0	0
10 - 20	4	1	25	0
20 - 30	6	2	33.3	0
30 - 40	9	4	44.5	1
40 - 50	12 (1)**	3 (1)**	25	(1)**
50 - 60	7 (3)	3 (2)	43	(2)
60 - 70	6 (2)	4 (1)	66.3	(1)
70 - 80	4 (4)	3 (3)	75	(3)
TOTAL	55 (10)	20 (7)	36	8 (7)

*All cases had preoperative Sinus Rhythm.

**Numbers in parenthesis indicate patients with carcinoma of esophagus.

suggested by the high incidence of auricular arrhythmias in our patients operated for carcinoma of the esophagus (Table I). Postoperative arrhythmias in this group may bear a relation to the manipulation of the esophagus as well as of the stomach considering that both these organs are very rich in sensory end organs connected to the vagi. Supportive evidence for such a mechanism could be the fact that auricular fibrillation developed in two patients of this group in whom only palliative gastrostomy was performed without opening of the thorax. Rapid shift of the mediastinum[1] did not appear to bear a relationship to the incidence of abnormal rhythms in the cases of Massie and Valle[15] and could be implicated in only one of our 20 cases. It is however possible that all these factors may act in conjunction and lead to the development of postoperative arrhythmias in extracardiac thoracic surgery.

The frequent occurrence of auricular fibrillation after mitral commissurotomy in contrast to other types of cardiac surgery, has to be ascribed to other factors particularly related to mitral disease. Dilatation of the left atrium in mitral stenosis has to be considered in first place as a factor *per se* causing auricular fibrillation.[14, 20] In addition rheumatic activity could play a role but no correlation has been established between the finding of Aschoff bodies in the amputated auricular appendix and the development of auricular arrhythmias.[8, 21] Another factor could be reabsorptive processes in the auricular incision associated with edema and necrosis at this site which may occur in the postoperative period[8, 9] and this could account for the variable time period that precedes the onset of auricular fibrillation after mitral surgery.

In all of our cases surgical pericarditis preceded or was detected simultaneously with the onset of arrhythmia. However, no clear relationship between the two events could be established since in seven patients sinus rhythm persisted despite development of postoperative pericarditis. Furthermore, the high incidence of auricular fibrillation in mitral surgery is in marked contrast to its low incidence in postoperative pericarditis in other types of cardiac surgery. Thus, in no instance did auricular fibrillation occur after pulmonary valvotomy and this is in keeping with the experience of others.[9] None of the above mentioned factors by itself appears adequate to explain all aspects of postoperative auricular arrhyth-

TABLE IV

TIME OF ONSET OF ARRHYTHMIA AFTER OPERATION

	Number of Cases
Within 5 days	15
Within 5 to 10 days	1
Within 10 to 20 days	3
After 20 days	1
TOTAL	20

mias in mitral stenosis but it is very likely that any of them, or the association of several such factors may act as a trigger in establishing a disturbance of rhythm in an atrium predisposed to it by disease.

Postoperative pericarditis. Pericardiotomy had been performed in all except one of our cases who developed pericarditis after surgery. The exception was a right pnemonectomy for bronchogenic carcinoma and here the pericarditis could be attributed to an inflammatory process secondary to abscess formation in the region of the carcinoma. Biocca *et al*[3] reported postoperative ST-T alterations in a high percentage of pneumonectomies in which the pericardium had to be incised in order to ligate the vascular root. The changes of the S-T segment as reported by Danese *et al*[6] were also, in all likelihood, secondary to pericarditis although no statement concerning pericardial incisions is made. Thus, from previous reports and our own experience it can be concluded that alterations of the electrocardiogram attributable to pericarditis can be anticipated in any case in which the pericardial sac was opened. This type of pericarditis seems to be directly related to surgical trauma.

Surgical pericarditis has been reported to have an early onset and to take a rapid course,[7, 9, 17] apparently more rapid than in other types of pericarditis. In some of our cases characteristic electrocardiographic alterations were seen to develop within a few hours. While the electrocardiographic pattern may follow the classical course of evolution extending over a period of three to four weeks, it was not unusual to see rapid regression of the acute alteration and rapid restitution to the preoperative pattern within one or two weeks, without the appearance of intermediate stages consisting of flattening and inversion of T waves. In digitalized patients, as in most cases submitted to mitral surgery, the postoperative electrocardiogram appears to be altered by the simultaneous action of two partly opposed factors: pericarditis tends to elevate the S-T segment while digitalis tends to depress and to shorten its duration. The result is a particular configuration of the final deflection, almost characteristic for electrocardiograms recorded shortly after mitral commissurotomy (Figs. 1 and 2).

SUMMARY AND CONCLUSIONS

1. Postoperative arrhythmias and pericarditis in 55 patients who underwent thoracic or cardiac surgery have been studied in the electrocardiogram.

2. Auricular fibrillation or flutter were the most common arrhythmias and occurred early after operation. Late onset, more than 10 days after surgery, suggests serious postoperative complications or reactivation of the rheumatic process. Auricular fibrillation develops frequently after surgery for carcinoma of the esophagus and seems to be associated with a grave prognosis.

3. The most important factors in the development of postoperative auricular fibrillation appear to be the age of the patient and preexistent pathology of the atrial myocardium. Hypoxemia and/or vagal irritation may trigger the abnormal mechanism.

4. Surgical pericarditis has an early onset and may follow the usual or an abbreviated electrocardiographic course. An electrocardiographic pattern is described of acute pericarditis modified by digitalis effect, characteristically seen in the first days after mitral commissurotomy.

Acknowledgment: We wish to thank the members of the Surgical Staff of the Michael Reese Hospital for the opportunity to use their records in this study, and to Dr. Louis N. Katz for his valuable criticism and suggestions.

RESUMEN

1. Se han estudiado los electrocardiogramas de las arritmias postoperatorias y en las pericarditis de 55 enfermos que sufrieron operaciones de tórax incluyendo cardíacas.

2. La fibrilación auricular o el flutter fueron las arritmias más comunes y se presentaron pronto después de las intervenciones. El principio tardío, más de 10 días después de la operación, sugiere complicaciones postoperatorias serias o reactivación de un proceso reumático. La fibrilación auricular se desarrolla frecuentemente después de cirugía por carcinoma del esófago y parece que denota un pronóstico grave.

3. Los factores más importantes en el desarrollo de la fibrilación auricular parecen ser la edad del enfrmo y la patología preexistente en el miocardio atrial. La hipoxemia y /o la irritación vagal pueden desencadenar el mecanismo anormal.

4. La pericarditis de origen quirúrgico tiene un principio temprano y puede seguir la evolución habitual o una evolución electrocardiográfica abreviada.

Son descritas las características de la pericarditis modificada por el efecto digitálico, característicamente vistas en los primeros días después de la comisurotomía mitral.

ZUSAMMENFASSUNG

1. Postoperative Arrhythmien und Pericarditis wurden im EKG an 55 Patienten untersucht, die einer thorakalen oder cardialen Operation unterzogen worden waren.

2. Vorhof-Flimmern oder Flattern waren die gewöhnlichsten Arrhytmien und traten bald nach der Operation auf. Spätes Auftreten, mehr als 10 Tage nach dem Eingriff, lässt auf ernsthafte postoperative Komplikationen schliessen oder auf eine Reaktivierung des rheumatischen Prozesses. Vorhof-Flimmern entwickelt sich häufig nach Eingriffen wegen Oesophagus-Carcinom und scheint mit einer schlechten Prognose verknüpft zu sein.

3. Die wichtigsten Faktoren beim Zustandekommen von postoperativem Vorhof-Flimmern scheinen das Alter des Kranken und bereits vorliegende pathologische Veränderungen des Vorhof-Myocards zu sein. Hypoxemie und Vagusreizung können den abnormen Mechanismus auslösen.

4. Chirurgische Pericarditis hat einen frühzeitigen Beginn und kann einen gewöhnlichen oder abgekürzten elektrocardiographischen Verlauf haben. Ein elektrocardiographischer Type einer akuten Pericarditis wird beschrieben, modifiziert durch Digitaliswirkung, mit charakteristischem Auftreten in den ersten Tagen nach Mitral-Commissurotomie.

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The Crossing of the Curves: Tuberculosis and Lung Cancer

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1. *Introduction*

The recent abrupt decline in tuberculosis mortality and the sharp rise in lung cancer mortality have led to a "Crossing of the Curves." (Chart 1). Primary cancer of the trachea, bronchus and lung by 1950 was causing more deaths than tuberculosis among persons 65 years of age and over. (Table I). Mortality statistics for 1954 show that lung cancer exceeds all forms of tuberculosis as a cause of death. Among California residents over 45 years of age, lung cancer now causes twice as many deaths as does tuberculosis. The experience in California is similar to that of the United States. (Chart 2).

Since 1930 tuberculosis mortality has dropped to one-tenth of its rate at that time, whether one considers all forms of the disease or respiratory tuberculosis alone. The respiratory cancer rate meanwhile, has more than trebled with lung cancer comprising an ever larger proportion of the total (Table I).

DEATH RATES PER 100,000 POPULATION, CALIFORNIA

	1930	1954
Tuberculosis, all forms	99.1	9.8
Tuberculosis, respiratory	88.4	9.0
Cancer, respiratory system	5.2	17.9

2. *Factors in the Reduction of Tuberculosis Mortality*

Two groups of factors have contributed to the decline in tuberculosis mortality. First are the medical developments specifically aimed at tuberculosis. These make possible earlier, more frequent and more valid diagnoses, and earlier treatment. Chief amongst them is more frequent resort to roentgenographic examination. The changeover from glass plates to film about the time of the first World War made x-raying a relatively dependable way of demonstrating pulmonary diseases. Popularization of the small film in this country in the early 40's provided speed and economy. The frequent finding of tuberculosis, sometimes in far advanced state, by routine hospital admission x-ray films has further stimulated physicians to suspect tuberculosis even though symptoms seem absent. Large campaigns to take many thousands of films of apparently well persons uncovered many new cases. Laboratory demonstration of the tubercle bacillus has found steadily increasing use. During the first 50 years of this century, over 100,000 tuberculosis beds were created in the United States. These

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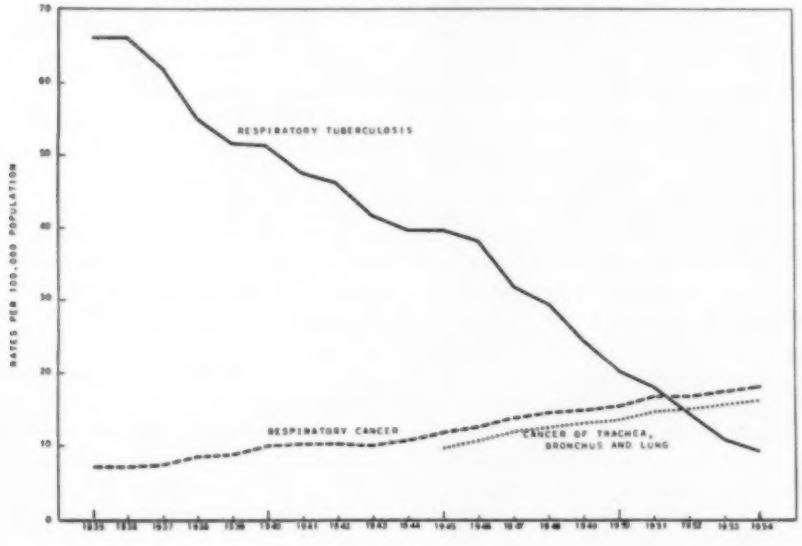
treatment facilities joined with increased use of collapse and excisional therapy, and especially the antibiotics that have come into effective use during the past decade, along with earlier diagnosis, have brought about the saving of many lives.

The second set of factors—general improvement in standard of living—is non-specific and relates only indirectly to tuberculosis control. Nevertheless, these factors may be more important than specific medical advances. Tuberculosis has always been more prevalent among people who live in conditions which define poverty, such as crowded housing and inadequate food. As Dubos[1] pointed out, industrialization of a country in its early stages brings about an increase in tuberculosis because of the herding of newly arrived, and presumably less immune, workers into crowded quarters. In later stages of industrialization, the lot of the worker improves, and so does his resistance to tuberculosis.

Both World Wars demonstrated this phenomenon of social dislocation plus overcrowding. People forced to live in combat-ravaged cities under grossly unsatisfactory conditions of housing and nutrition experienced a rapid increase in tuberculosis cases and deaths, which just as quickly subsided when peace brought its healing.

The combination of specific and general factors in this country has resulted in a steady decline in tuberculosis mortality since before the turn of the century, a decline which was accelerated after each world war. The addition of antibiotics and other potent drugs to the therapeutic re-

CHART 1
DEATH RATES FROM RESPIRATORY TUBERCULOSIS AND RESPIRATORY CANCER, 1935-1954, AND CANCER OF THE TRACHEA, BRONCHUS AND LUNG, 1945-1954, CALIFORNIA
(BY PLACE OF OCCURRENCE 1935-1941; BY PLACE OF RESIDENCE 1942-1954)



SOURCE: CALIFORNIA STATE DEPARTMENT OF PUBLIC HEALTH, DEATH RECORDS

TABLE I

DEATHS DUE TO TUBERCULOSIS AND CANCER OF RESPIRATORY SYSTEM BY AGE GROUP, CALIFORNIA, 1935, 1940, 1945, 1950-1954
(1935, 1940 by place of occurrence. 1945, 1950-1954 by place of residence)

Cause of Death and Age Group	Number									Rate[1]		
	1930	1935	1940	1945	1950	1951	1952	1953	1954	1940	1950	1954
Tuberculosis, all forms	5,657	4,496	3,887	3,801	2,301	2,160	1,789	1,373	1,223	56.3	21.7	9.8
Under 45	NA	NA	2,015	1,892	876	774	569	382	307	42.4	11.8	....
45 - 64	NA	NA	1,395	1,357	933	849	750	563	495	87.5	41.5	....
65 and over	NA	NA	473	552	491	537	468	427	420	85.2	54.9	....
Tuberculosis, respiratory	5,047	4,085	3,544	3,502	2,114	1,982	1,654	1,275	1,115	51.3	20.0	9.0
Under 45	NA	NA	1,774	1,658	751	654	491	332	260	37.3	10.1	....
45 - 64	NA	NA	1,320	1,310	896	810	709	533	462	82.8	39.8	....
65 and over	NA	NA	446	534	466	518	452	409	392	80.3	52.1	....
Cancer, respiratory system	296	447	686[a]	1,038	1,614	1,824	1,918	2,089	2 224	9.9	15.2	17.9
Under 45	NA	NA	74	114	115	105	106	161	121	1.6	1.5	....
45 - 64	NA	NA	403	579	834	923	1,002	1,080	1,112	25.3	37.1	....
65 and over	NA	NA	209	345	662	796	810	848	991	37.6	74.0	....
Cancer, trachea, bronchus and lung	NA	NA	525[a]	857	1,418	1,607	1,719	1,861	2,020	7.6	13.4	16.2
Under 45	NA	NA	52	96	101	89	92	142	109	1.1	1.4	....
45 - 64	NA	NA	326	488	745	827	913	975	1,027	20.4	33.1	....
65 and over	NA	NA	147	273	569	691	714	744	884	26.5	63.6	....

NA Not available.

[1]Rate per 100,000 enumerated population.

[a]By place of residence.

Totals include 8 deaths with age not stated.

Source: U. S. Bureaus of Census, *Mortality Statistics, 1935*, Table 6, p. 144.
Ibid., *Vital Statistics of the United States, 1940*, Part I, Table 13, p. 277.
State of California, Department of Finance, Population Estimates, 1954.
State of California, Department of Public Health, Death Records.

sources has made the rate of decline become increasingly steep during the past few years. The annual incidence rate has likewise decreased, but at a less rapid rate. In this connection one must note that the tremendous expansion of x-ray survey programs has increased the proportion of known tuberculosis. Nevertheless, since there are still an estimated 150,000[2] unreported and largely undiagnosed and unsuspected persons with active tuberculosis in the U.S., diagnostic activities and propaganda for more frequent x-ray films, particularly for the more vulnerable segments of the population, must continue unabated.

A gradual change in the differential diagnostic problem is evident. In past years, tuberculosis was found more commonly on the chest film than all other serious chronic lung conditions combined. Today, lung cancer and lung suppuration challenge tuberculosis in frequency. With the continuing decrease in tuberculosis, lung disease of other etiology, especially lung cancer, will dominate the diagnostic stage more and more.

3. *Factors in the Increase of Lung Cancer Mortality*

Because so few patients with lung cancer survive even with treatment, the age-adjusted mortality rate remains the best measure of the disease. This rate is still increasing rapidly.

Do improved methods of diagnosis account for the rise in lung cancer deaths? Undoubtedly the more widespread use of x-ray film examinations bronchoscopy, exploratory thoracotomy, biopsies, autopsies—and most recently, cytologic tests—have improved the diagnosis of the disease. However, since 1940, the mortality rate for men in California has increased 147 per cent while the increase for women has been only 29 per cent. (Table I). Can one assume that physicians apply their diagnostic techniques so much more completely to men than to women? In addition, analyses of autopsy series in several hospitals (with a consistently high autopsy ratio for many years) reveal that the proportion of deaths due to lung cancer has increased spectacularly during the past few decades. Substantial evidence thus indicates that this is a disease which is truly increasing, and rapidly. One must, therefore, look about for some explanation of the phenomenon. Three sets of factors have been suggested and present data indicate that each of the three play a role in the development of lung cancer.

Many studies[3] have disclosed a much greater frequency of cigarette smoking, especially heavy cigarette smoking, among patients with lung cancer as compared with controls (usually hospitalized patients without cancer but of the same age and sex as the case series).

Several occupations have been incriminated, particularly those involving exposure to certain metallic substances or fumes. Over half the workers in some European mines with radio-active ores have in times past succumbed to lung cancer.[4] In this country, men exposed to certain chromate ore operations suffer a mortality from lung cancer 16 times as great as that of a similarly aged group of men in the general population.[5] A recent investigation[6] has implicated: welding; overhead crane operators in metal

TABLE II

DEATHS DUE TO TUBERCULOSIS AND CANCER OF RESPIRATORY SYSTEM, MALES BY AGE GROUP
CALIFORNIA, 1935, 1940, 1945, 1950-1954
(1935, 1940 by place of occurrence. 1945, 1950-1954 by place of residence)

Cause of Death and Age Group	Number								Rate[1]		
	1935	1940	1945	1950	1951	1952	1953	1954	1940	1950	1954
Tuberculosis, all forms	2,887	2,616	2,552	1,647	1,552	1,294	1,015	925	94.4	31.1	14.9
Under 45	NA	1,131	1,018	479	403	309	204	182	46.5	12.8	....
45 - 64	NA	1,130	1,101	774	705	615	469	413	137.5	68.2	....
65 and over	NA	351	433	393	444	368	341	329	134.6	96.1	....
Tuberculosis, respiratory	2,634	2,413	2,391	1,530	1,449	1,211	957	855	68.6	28.9	13.8
Under 45	NA	997	900	407	342	265	179	153	41.0	10.8	....
45 - 64	NA	1,079	1,069	747	679	587	448	387	131.3	65.8	....
65 and over	NA	333	422	375	428	357	329	314	127.7	91.7	....
Cancer, respiratory system	NA	529[a]	816	1,322	1,499	1,587	1,747	1,871	15.0	25.0	30.2
Under 45	NA	56	87	83	70	76	117	95	2.3	2.2	....
45 - 64	NA	316	469	722	791	859	944	968	38.4	63.6	....
65 and over	NA	157	260	514	638	652	686	808	60.2	125.7	....
Cancer, trachea, bronchus and lung	NA	395[a]	672	1,161	1,324	1,426	1,564	1,713	11.2	21.9	27.7
Under 45	NA	56	87	75	60	69	104	84	1.6	2.0	....
45 - 64	NA	249	395	644	711	782	855	899	30.3	56.8	....
65 and over	NA	107	201	439	553	575	605	730	41.0	107.3	....

Not available.
[1]Rate per 100,000 enumerated population.
[a]By place of residence.
Totals include 12 deaths with age not stated.

Source: U. S. Bureau of the Census, *Mortality Statistics, 1935*, Table 6, p. 144.
Ibid. *Vital Statistics of the United States, 1940*, Part I, Table 13, p. 277.
State of California, Department of Public Health, Death Records.

industries; lead, zinc and copper mining; and other occupations.

Stocks[7] in England has demonstrated that cities with diminished sunlight at ground level (presumably due to air pollution) have a substantially higher lung cancer mortality rate than do cities with greater sunlight. Waller[8] in England and Kotin[9] in this country have isolated carcinogenic substances from polluted city air.

In evaluating the carcinogenic effects of environmental agents one must constantly bear in mind the time factor. The evidence suggests that environmental factors lead to human cancer only after many years of exposure. Hence, the rise in lung cancer mortality during the period 1930-1960 may reflect environmental factors and changes during all of the first half of this century. Likewise the environmental changes during recent years—e.g., vast increase in cigarette smoking among women and among young people of both sexes, entry of hundreds of thousands of persons into such occupations as welding, the heavy air pollution of certain cities—may portend a continuing increase in lung cancer mortality during the latter half of this century. The slight relative increase in lung cancer among women during the past few years may be the beginning of such a trend.

It is clear that some environmental changes must have acted with great effect to produce the rise in lung cancer during the past two decades. If we are to control the disease by preventive measures we must identify and remove the causative factors which are acting *now*, as well as those which can be incriminated from the past. The need of new knowledge and action arises in part from the fact that control measures undertaken at the present time would begin to exert significant effect only 10 to 30 years hence. We now have no way of stopping the effect of cigarette smoke, polluted air, or carcinogenic factors inhaled in the past.

4. *Comparisons Between Tuberculosis and Lung Cancer Mortality Patterns*

A. Sex. The male predominates in mortality from both conditions. (Table II and III). The ratio is about three to one in the case of tuberculosis, and five to one in lung carcinoma. In the case of tuberculosis, this represents a substantial change since the ratio in earlier years was approximately 1:1 at the beginning of the century.

B. Age. In the early part of the century, tuberculosis was a disease of adolescents and young adults predominately. It has now become a disease of middle aged and older persons predominately. Some of this change may be explained by the cohort concept—the heavily infected younger generation of the 20's living through subsequent decades but with frequent and often fatal relapses. Deaths from tuberculosis before the age of 20 have become quite uncommon, and even among women at the early childbearing ages, there has been great reduction. Lung cancer, too—like most cancers—is a disease of the middle and later years of life.

C. Social groups. Tuberculosis is especially prevalent in slum areas, amongst poorly nourished persons, (such as chronic alcoholics), and amongst those living in contact with infectious cases. Lung carcinomas are more scattered in their distribution; housing and nutritional factors seem to play little, if any, role. Smokers cannot be considered a "social

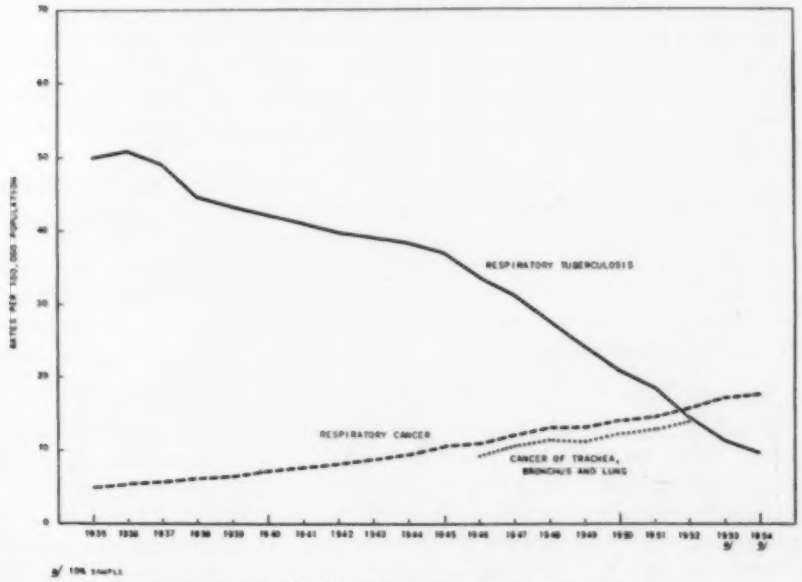
group", since the addiction cuts through all classes. However, there is evidence that certain occupational groups are more frequently attacked by lung cancer.

5. *Diagnosis and Treatment in the Control of Tuberculosis and Lung Cancer*

Ordinarily, an x-ray film of the chest is the earliest method of detecting either disease. However, certain forms of tuberculosis and carcinoma cannot be easily differentiated on the film (e.g., isolated, hard, round nodule!). In fact, the x-ray film usually cannot be considered definitively diagnostic unless supplemented by laboratory methods and histologic examination. In the case of tuberculosis, the demonstration of tubercle bacilli is definitive. In the case of carcinoma, biopsy or cytologic examination may give the answer. However, often all such tests are negative and thoracotomy must be undertaken for direct observation and palpation of the lesion. Even so, if doubt continues, resection is carried out and the final diagnosis is not known until the pathologist's report is made. The classic hard, round nodule more often turns out to be tuberculosis than cancer, but the hazard to life of a carcinoma is so great as to justify resectional therapy. With the passage of time, physicians are resorting more and more to diagnostic thoracotomies and less to the philosophy of "waiting to see what will happen" in the serial films. Every clinically silent lesion casting shadow on the chest x-ray film must have tuberculosis and carcinoma ruled out before any other diagnosis can safely be made, and resection of lung containing a small cancerous nodule in a person in

CHART 2

DEATH RATES FROM RESPIRATORY TUBERCULOSIS AND RESPIRATORY CANCER, 1935-1954, AND CANCER OF THE TRACHEA, BRONCHUS AND LUNG 1946-1952, UNITED STATES (BY PLACE OF OCCURRENCE 1935-1941, BY PLACE OF RESIDENCE 1942-1954)



a/ 10% SAMPLE

SOURCE: BUREAU OF THE CENSUS, UNITED STATES PUBLIC HEALTH SERVICE, NATIONAL OFFICE OF VITAL STATISTICS

apparently good health represents a triumph of preventive medicine.

As thoracic surgery became progressively more important in the treatment of pulmonary tuberculosis, many hospitals and sanatoriums created separate departments for this purpose. As resectional operative procedures became commoner, in many places patients with nontuberculous chest diseases were also admitted for treatment—particularly bronchiectasis and cancer of the lung. The same operative set-up can be used for operative treatment of tuberculosis or cancer. Similar precautions are necessary in regard to anesthesia and immediate postoperative care. As time goes on, many thoracic surgery departments particularly those connected with general hospitals, are devoting a larger proportion of their time to the treatment of malignancy rather than tuberculosis, and of course, the ever broadening field of cardiac surgery has increased its share.

Chest diagnostic centers, in institutions, at public health clinics and at university centers, are processing ever larger numbers of cases which turn out to be cancer, although originally sent in as suspect tuberculosis or other non-malignant disease. Here, too, an organization originally set up to diagnose and often to treat tuberculosis has found that cancer plays a more important and sometimes a predominating role.

Mass x-ray surveys were set up primarily for the early diagnosis of unsuspected tuberculosis. But, of course, other diseases of lung and heart were revealed. Cancer showed a relatively small but consistent prevalence (Churchill, Guiss). In tuberculosis control there is no question of the value of this mass approach, especially in selected groups. As a weapon in the early diagnosis of lung cancer, the mass approach has been suggested for older men, especially smokers.

The programs of medical meetings and conventions show ever growing numbers of papers concerning problems of cancer of the lung— its diagnosis, its treatment and more recently its epidemiology. In the latter connection health departments, all of which have long participated in tuberculosis control, are now finding their interest spreading to the related field of cancer of the lung.

Thus, it is evident that the organization and technical machinery originally set up for tuberculosis can be and is being used in increased proportion in attacking the problem of cancer of the lung. The same skills are necessary for diagnosis and treatment. As time goes on and study reveals ever more suggested correlations, the epidemiology of cancer of the lung will likewise assume a larger importance, and this will be of concern to all health departments.

6. *Epidemiologic Approaches to Control*

The final conquest of tuberculosis depends upon eradication of the root causes which underlie the transmission of infection from one person to another. Elimination of slums will continue. But slum and other blighted neighborhoods, whether urban or rural, will continue to be the areas of special concern in the search for tuberculosis. The thorough examination of every domiciliary and occupational contact of tuberculosis cases and

TABLE III

DEATHS DUE TO TUBERCULOSIS AND CANCER OF RESPIRATORY SYSTEM
FEMALES BY AGE GROUP
CALIFORNIA, 1935, 1940, 1945, 1950-1954
(1935, 1940 by place of occurrence. 1945, 1950-1954 by place of residence)

Cause of Death and Age Group	Number								Rate[1]		
	1935	1940	1945	1950	1951	1952	1953	1954	1940	1950	1954
Tuberculosis, all forms	1,609	1,271	1,249	654	608	495	358	298	37.5	12.4	4.8
Under 45	NA	884	874	397	371	260	178	125	38.0	10.8	....
45 - 64	NA	265	256	159	144	135	94	82	34.3	14.3	....
65 and over	NA	122	119	98	93	100	86	91	41.4	20.2	....
Tuberculosis, respiratory	1,451	1,131	1,111	584	533	443	318	260	33.3	11.0	4.2
Under 45	NA	777	758	344	312	226	153	107	33.4	9.3	....
45 - 64	NA	241	241	149	131	122	85	75	31.2	13.4	....
65 and over	NA	113	112	91	90	95	80	78	38.4	18.7	....
Cancer, respiratory system	NA	157[a]	222	292	325	331	342	353	4.6	5.5	5.6
Under 45	NA	18	27	32	35	30	44	26	0.8	0.9	....
45 - 64	NA	87	110	112	132	143	136	144	11.3	10.0	....
65 and over	NA	52	85	148	158	158	162	183	17.7	30.5	....
Cancer, trachea, bronchus and lung	NA	130[a]	185	257	283	293	297	307	3.8	4.9	4.9
Under 45	NA	13	20	26	29	23	38	25	0.6	0.7	....
45 - 64	NA	77	93	101	116	131	120	128	10.0	9.1	....
65 and over	NA	40	72	130	138	139	139	154	13.6	26.7	....

NA Not available.

[1]Rate per 100,000 enumerated population.

[a]By place of residence.

Source: U. S. Bureau of the Census. *Mortality Statistics' 1935*, Table 6, p. 144.
Ibid., *Vital Statistics of the United States, 1940*, Part I, Table 13, p. 277.
State of California, Department of Public Health, Death Records.

the x-ray film examination of every hospital and prison admission must be pursued with increasing intensity. All the persons who are discovered in these diagnostic nets must be treated and the infectious ones isolated preferably in a hospital. This will cut so many chains of person-to-person infection that, even in the absence of really effective therapy, virtual disappearance of the disease may be hoped for. Since near elimination of tuberculous cattle in the U.S.A., only homo sapiens is a significant carrier of tuberculosis. The carriers must be identified and separated until they become non-infectious.

The factor of resistance is a very important one in tuberculosis. Improvement in general status of health and less crowding both make transmission less likely, even in the presence of an infectious individual.

A continuing significant factor in tuberculosis control is alcoholism, which increases chances of transmission and reduces resistance. As time goes on, an ever greater proportion of the tuberculosis burden will be found in slum areas in which alcoholism, likewise, is an important problem.

No dependable data is at hand regarding the role of smoking in tuberculosis. However, respiratory trauma, which is inevitable in a coughing, compulsive smoker, probably decreases the ability of pulmonary tissue to defend itself against the tubercle bacillus—or any type of infection for that matter. Many physicians unfortunately do not go to the trouble of aiding their patients in stopping the smoking habit while taking the cure for tuberculosis.

Only during recent years has medical and epidemiological opinion begun to shift toward the idea that lung cancer, at least in high proportion, is environmentally caused. Investigations in many parts of the world are now bringing data to bear which support this conclusion.

Some persons still hold that until the precise substance in tobacco smoke which causes lung cancer can be demonstrated, and unless lung cancer can be consistently produced in small animals by exposing them to tobacco smoke or substances derived therefrom, we cannot consider cigarette smoking to be a cause of lung cancer. Suppose the same type of reasoning were applied to any other demonstration by epidemiological means of an environmental agent as a causative factor in the disease. It is useful to recall in this connection the situation of Sir John Snow in the early 1850's. At that time he demonstrated that one's chances of developing cholera in London were vastly increased by drinking water from certain polluted supplies. He concluded, and correctly, that drinking such polluted water was a causative factor in cholera—on the basis of epidemiologic evidence. It was some years later before the germ theory of disease was established and almost a half century before the Vibrio comma was isolated as the specific etiological agent. Should health authorities have waited that half century before undertaking the purification of water supplies?

The situation today in regard to lung cancer is comparable. Overwhelming epidemiological evidence now indicates that cigarette smoking is an important causative factor in lung cancer. Further studies should, of course, be carried out. This is necessary to overcome the last lingering

doubts among conservative epidemiologists and physicians. Even more epidemiologic study is needed of air pollution and occupations as causative factors in lung cancer. It is conceivable that cigarette smoking may have been the most important causative factor for the increasing mortality from lung cancer up to the present time, but that other environmental agents may be acting now to push this disease still higher in the ranks of causes of death.

Laboratory studies should be carried out to isolate the specific substances in the environmental agents and the mechanisms of action. However, those looking to laboratory work as the sole means of demonstrating a causative agent should reflect on the history of our knowledge of the vitamins in nutrition. It must also be remembered that the tissues of small animals react differently from the tissues of man. In particular the mouse does not seem to be subject to the same histological type of lung cancer as does man. Laboratory work is certainly not to be deprecated. On the contrary, it should be pursued with intensified vigor. But let it be placed in appropriate perspective to other kinds of studies of disease among human populations.

In summary, in respect to lung cancer let us (1) pursue epidemiological knowledge, (2) act upon this knowledge as it becomes available—through health education and other means; and (3) undertake laboratory investigation to amplify our knowledge of causative factors in lung cancer.

SUMMARY

Among the serious chronic pulmonary diseases, cancer of the lung is challenging tuberculosis in frequency and has already surpassed it in mortality.

Essentially the same case-finding, diagnostic, and surgical machinery can be employed against the two diseases. As in the case of tuberculosis, cancer of the lung is revealing an epidemiologic pattern which may prove helpful in the understanding and control of the disease. Just as tuberculosis once had to be considered in the differential diagnosis of every case of chronic pulmonary disease, so today must cancer always receive consideration. No obscure lung disease can be considered as satisfactorily assessed until cancer has been excluded.

RESUMEN

Entre las enfermedades crónicas pulmonares serias, el cáncer del pulmón compite ya con la tuberculosis en frecuencia y ya ha sobrepasado a la tuberculosis en mortalidad.

En esencia los mismos procedimientos de búsqueda, diagnóstico, y quirúrgico pueden emplearse contra las dos enfermedades. Como en el caso de la tuberculosis, el cáncer del pulmón está revelando un aspecto epidemiológico que puede ser útil de considerarse para la comprensión y el control de la enfermedad.

Así como la tuberculosis tiene que considerarse en el diagnóstico diferencial en todo caso de enfermedad crónica pulmonar, el cáncer debe ahora

merecer consideración. Ninguna enfermedad obscura del pulmón puede estimarse como bien estudiada hasta que el cáncer haya sido excluído satisfactoriamente.

RESUME

Parmi les affections pulmonaires chroniques graves, le cancer du poumon concurrence la tuberculose en fréquence, et l'à déjà dépassée en mortalité.

Dans l'ensemble, les méthodes de détection de la maladie, les procédés de diagnostic et les techniques chirurgicales sont communs aux deux affections. Comme pour la tuberculose, le cancer du poumon présente des caractéres épidémiologiques qui peuvent se révéler frucutueux pour l'étude de l'affection et pour diriger la lutte contre elle. De même qu'on devait autrefois penser à la tuberculose dans le diagnostic différentiel de toutes les affections pulmonaires chroniques, on doit toujours avoir le diagnostic de cancer présent à l'esprit. Le diagnostic d'aucune affection pulmonaire de cause indéterminée ne peut être considéré comme ayant été suffisamment précisé tant que l'on n'a pas éliminé le cancer.

ZUSAMMENFASSUNG

Unter den ernsthaften chronischen Lungenkrankheiten bleibt der Lungenkrebs an Häufigkeit nicht hinter der Tuberkulose zurück und hat sie bereits hinsichtlich der Mortalität übertroffen.

Es können im wesentlichen die gleichen Einrichtungen hinsichtlich Fallsuche, Diagnostik und operativem Vorgehen für beide Krankheite benutzt werden. Wie im Falle der Tuberkulose zeight der Krebs der Lunge eine epidemiologische Form, die sich als Hilfe für das Verständnis und die Bekämpfung der Erkrankung erweisen kann. In der gleichen Wiese wie einst die Tuberkulose in Betracht zu ziehen gewesen ist bei der Differentialdiagnose eines jeden Falles von chronischer Lungenkrankheit, so muss heute immer der Krebs erwogen werden. Keine unbekannte Lungenkrankheit kann als ausreichend beurteilt angesehen werden, so lange nicht der Krebs ausgeschlossen worden ist.

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Prevalence of Sensitivity to Coccidioidin, With Special Reference to Specific and Nonspecific Reactions to Coccidioidin and to Histoplasmin*

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Geographic variation in the prevalence of coccidioidomycosis has aroused increasing interest in recent years, particularly since the experience of the Armed Forces during the second world war confirmed earlier indications that the fungus infection was endemic not only in southern California but also in Arizona, New Mexico and western Texas.[1-3] Before that time, in fact before the identification by Dickson and Gifford[4, 5] of "San Joaquin Valley Fever" as a benign primary form of coccidioidomycosis, cases of coccidioidal granuloma had already been reported from Texas.[6-8] By 1940 cases had also been reported from other parts of the southwest;[9-12] and the epidemiological studies of Aronson and his associates[13] published in 1942 substantiated the likelihood that coccidioidal infection was highly prevalent in certain parts of Arizona.

The importance of coccidioidomycosis as a cause of pulmonary disease was clearly demonstrated by observations made on large numbers of military personnel brought into the arid regions of the southwest for training during the war. Several thousand became infected and as an appreciable number developed clinical disease medical officers soon recognized that coccidioidomycosis had to be considered in the differential diagnosis of patients with pulmonary disease. It was also recognized that the problem was not entirely confined to residents of the southwest, as infection acquired during a brief period in the endemic area, or even just traveling through it, may develop into clinical disease after the patient had left the endemic area.[14-16]

The close parallelism between coccidioidomycosis and histoplasmosis is of course now well known. Each appears to be endemic in fairly distinct and different geographic localities. Both are predominantly benign infections and only rarely cause progressive disease; although both can produce x-ray evidence of pulmonary infiltration and calcification; and both produce skin sensitivity to the homologous antigen, but not to tuberculin. Though mycologic and serologic tests are generally needed to establish

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the diagnosis of clinical disease, the coccidioidin and histoplasmin skin tests are widely used to establish evidence of infection.

The purpose of the present paper is to give for the country as a whole a broad picture of the geographic distribution of skin sensitivity to coccidioidin. Although the prevalence of coccidioidin sensitivity in certain counties of some states has been defined in greater detail by other workers,[17-21] the present material provides comparisons of prevalence rates derived from uniform observations on lifetime residents of nearly every state in the union. In addition, results of simultaneous histoplasmin tests are available for a study of specific and nonspecific reactions to both coccidioidin and histoplasmin in different localities.

Material and Methods

Material is available for three groups of young adults, totalling about 110,000 persons, most of them tested simultaneously with coccidioidin, histoplasmin and tuberculin. Reports of the histoplasmin and tuberculin test results have been published elsewhere,[22, 23] together with details about the persons tested and the procedures used. The pertinent points need only be briefly summarized here.

Geographically the broadest coverage was obtained from the testing of over 88,000 young men in cooperation with the U.S. Navy at the Naval Training Center at San Diego, California, during the years 1949-51. Systematic efforts were made to see that each new recruit was tested as he entered the training center. The testing was done by a small group of medical corpsmen, instructed and periodically supervised by the field research staff of the Tuberculosis Program. As the San Diego Naval Training Center drew recruits from all but the North Atlantic and Great Lakes regions, the test results provide uniform observations with which to compare frequencies of reactors from county to county throughout a large part of the country. Observational errors and variations in technique (although greater than had been expected) are, we believe, distributed at random and without regard to geographic place of residence of the recruits.

Another group, consisting of more than 4,000 students, both men and women, were tested with all three antigens during the years 1948 and 1949 at two universities in the Great Lakes region and, in 1950, in a number of colleges in New England. Testing at the two universities was done by the Student Health Officers in the schools; testing in the New England colleges by a Tuberculosis Program field research team.

The third group of young adults for whom data are available consists of about 17,000 student nurses, all women, tested during the years 1945-49 while attending 76 training schools located in ten metropolitan areas throughout the country.[24] Almost all of the tests were done by two nurses who were specially trained in the technique of giving and reading skin tests and who travelled from school to school at six-month intervals throughout the period of the study to do the testing.

Tests in all three groups were given by intradermal injection of 0.1 ml. of a 1:100 dilution of coccidioidin. The product identified as C-24, pre-

pared by Dr. C. E. Smith, was used for the student nurses, the college students and most of the Navy recruits. Batch C-29-31 (Dr. Smith) was used for recruits tested in 1951. Reactions were read at 48 to 96 hours by measuring the transverse diameter of induration with a millimeter ruler. The same technique was used for simultaneous tests with histoplasmin. All except some of the student nurses were tested with one of three lots of histoplasmin identified as H-15, H-40 or H-42, prepared by Dr. Arden Howell, Jr. of the Public Health Service. Lots H-40 and H-42 were both standardized against H-15 and the dilution adjusted to be equivalent to a 1:1000 dilution of H-15.[25] H-3 (Dr. C. W. Emmons) and several other batches (Dr. Howell) were used during the early years of the student nurse program.

At the time of testing, each person was requested to give a complete residence history by listing in chronological order each city or county in which he had lived for six months or more since birth. All those who had spent their entire lifetime in one county or had not been away from their home county for more than six months, were later classified as "one-county residents."

The geographic distribution of coccidioidin sensitivity is based only on the findings in one-county residents. For greater homogeneity, the results are further limited to white men and women who were between 17 and 21 years of age at the time of testing. Basic data for the entire study population are set forth in Table I, which gives the groups from which more than 48,000 one-county residents were drawn for mapping the geographic variations in prevalence of coccidioidin sensitivity, and the numbers excluded for reasons of age, race or multiple county residence.

Prevalence of Coccidioidin Sensitivity

A broad picture of the prevalence of coccidioidin sensitivity in young adults throughout the nation is given in the map in Figure 1, with increasing levels indicated by successively darker shading. For contrast and

TABLE I
TOTAL NUMBER OF PERSONS TESTED WITH COCCIDIOIDIN, NUMBER EXCLUDED AND NUMBER INCLUDED IN PRESENT REPORT BY STUDY GROUP

Study Population	Total Number Tested	Multiple County Residents (Excluded)	One County Residents	
			Not 17-21 Years or Not White (Excluded)	Age 17-21 Years and White (Included)
Total	110,601	60,551	1,374	48,676
Male	91,089	50,397	910	39,782
Female	19,512	10,154	464	8,894
Navy Recruits (male)	88,916	49,074	741	39,101
College students				
Male	2,173	1,323	169	681
Female	2,276	1,077	132	1,067
Student Nurses (female)	17,236	9,077	332	7,827

comparison, the prevalence of sensitivity to histoplasmin in essentially the same study population (more persons were tested with histoplasmin than with coccidioidin) is reproduced in Figure 2 from a previous report.[22]

Both maps are based only on the results for lifetime one-county residents; and the prevalence of sensitivity is expressed as the percentage of positive reactions. A positive reaction is defined in this instance as an induration measuring 5 mm. or more although, as will be shown later, the use of that commonly accepted criterion is not satisfactory in some localities, even for lifetime residents, for estimating the prevalence of specific infection. As a number of counties were represented by too few persons to provide stable figures, a moving average was used and, in some instances, further adjustment was made to reduce gross variations owing to small numbers. Details of the procedure used to prepare both maps are given in the report on histoplasmin sensitivity.[22]

As shown in Figure 1, the geographic localization of appreciable frequencies of coccidioidin reactors in the southwestern part of the country is immediately apparent. Rates exceeding 50 per cent appear only in three states: California, Arizona and Texas. The area of highest frequency in California comprises Kern, Kings and Tulare Counties in the heart of the San Joaquin Valley—the locality in which "Valley Fever" was originally described as an endemic disease. In Arizona and Texas the highest rates are found in counties toward the south, along the Mexican border. The rates drop sharply toward the north, falling below 30 per cent in many of the adjacent counties and, within a distance of a few hundred miles, below 10 per cent. Throughout the rest of the country the rates are very low, not exceeding 5 per cent across the central area and into New England,

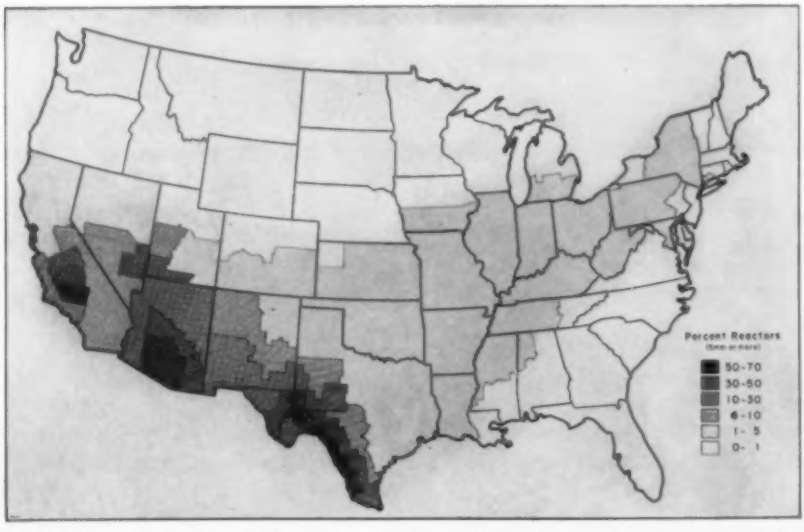

FIGURE 1: Distribution of counties and groups of counties by frequency of coccidioidin reactors in 48,676 young adults.

and less than 1 per cent in the north, northwest and southeast.

The focal area of coccidioidin sensitivity within this country thus appears to stretch along the Mexican border states from California to Texas, including the southern parts of Nevada and Utah. Across the border, in northern Mexico, the rates are also high, as reported by Glusker and his associates.[26] Among 7,000 Mexican Army recruits, the highest frequency of coccidioidin reactors—67 per cent—was found in lifetime residents of the State of Sonora, just south and west of Arizona. The next highest rates were found in recruits from Chihuahua, the state that borders on Arizona, New Mexico and western Texas; from Colima toward the south, on the coast; and from Baja California. Of the four states in Mexico with the highest rates, three are located along the Mexican-U.S. border.

Histoplasmin sensitivity, as shown in Figure 2, is highly prevalent in the east central part of the United States, where the frequency of reactors exceeds 80 per cent in a number of states. The areas of high frequency are surrounded by concentric rings of lesser frequencies, and the rates finally become negligible along the eastern seaboard and in most of the western part of the country.

Comparison of the patterns exhibited by the two maps shows an overlapping in some localities. The area with high histoplasmin rates is shadowed on the coccidioidin map by frequencies of 1 to 5 per cent coccidioidin reactors. And the high coccidioidin areas in the southwest show appreciable frequencies of histoplasmin reactors. It is therefore necessary to consider how the prevalence of sensitivity shown on the maps is affected by nonspecific reactions to the two fungus antigens.

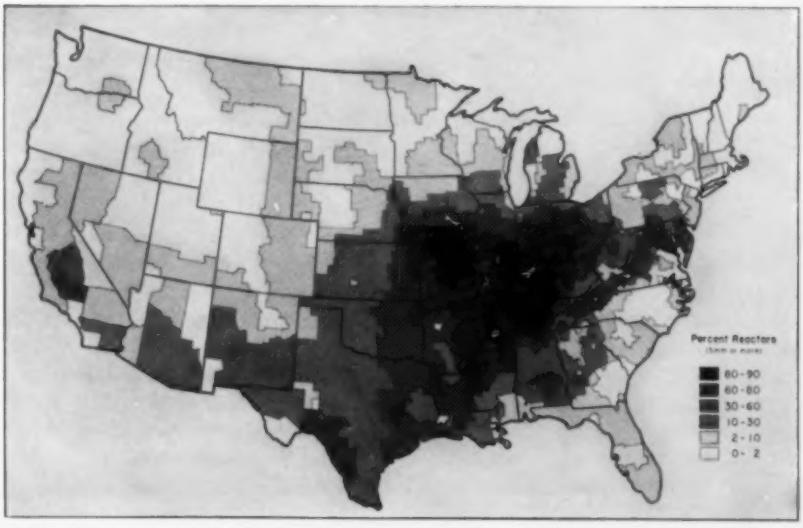

FIGURE 2: Distribution of counties and groups of counties by frequency of histoplasmin reactors in 68,452 young adults. (Reproduced from article "Geographic Variation in the Prevalence of Histoplasmin Sensitivity," by Manos et al, *Dis. Chest*, 29:6, June, 1956.)

General Aspects of the Correlation Between Coccidioidin and Histoplasmin Reactions

The relation between skin reactions to coccidioidin and histoplasmin can readily be studied in the laboratory by giving both coccidioidin and histoplasmin tests to four different groups of animals: one group known not to be infected with either Coccidioides or Histoplasma (or any other antigenically related organism), one infected with Histoplasma but not Coccidioides, one infected with Coccidioides but not Histoplasma, and finally, one group known to be infected with both. Emmons and his associates,[27, 35] Howell,[28] and others, have demonstrated an association between sensitivity to coccidioidin and histoplasmin as well as other antigens, including haplosporangin and blastomycin. Each of these antigens produces reactions referred to as specific in animals sensitized by infection with the corresponding or homologous fungus; each may also produce nonspecific reactions in animals sensitized by infection with some other (heterologous) fungus. When the identity of the sensitizing agent is known, as is usually the case in laboratory experiments, the nonspecific reactions may be further defined as cross-reactions. Thus, for example, a reaction to histoplasmin in an animal infected by Coccidioides may be explicitly designated as a histoplasmin cross-reaction owing to sensitization by Coccidioides.

The study of specific and nonspecific reactions in human beings is more difficult and can almost never be as definitive as in laboratory animals. Only rarely, and in special situations, is it possible to know with certainty the identity of the infecting organism, or even to be certain that there is only a single infecting organism. In human beings it is therefore seldom possible to speak of cross-reactions—the broader term nonspecific being more generally applicable. Despite the obvious limitations of studies in humans as compared with experimental animals, the work particularly of Smith,[29] Loosli,[30] Furcolow,[20] and their associates, has shown that results of testing with histoplasmin and coccidioidin generally parallel those from the laboratory. Specific as well as nonspecific reactions may be obtained with either antigen; but nonspecific coccidioidin reactions in presumably Histoplasma-infected persons appear to be less frequent than nonspecific histoplasmin reactions in persons with coccidioidal infection.

Material available for the present study can yield additional information on the nature of specific and nonspecific reactions to histoplasmin and coccidioidin. Based on our present knowledge of the endemic foci of the two fungus infections, the reactions of lifetime residents of three different geographic areas have been selected for detailed analysis. One group comprises recruits from the northwest, where infection with either Histoplasma or Coccidioides is unlikely; one from the eastcentral area, where histoplasmal infection is common but coccidioidal infection is not; and one from the southwest where coccidioidal infection is endemic but histoplasmal infection apparently is not.

Results of coccidioidin and histoplasmin tests for nearly 23,000 Navy recruits are given in appendix Tables A, B and C as correlations of the sizes of the transverse diameter of induration of reactions to each antigen.

Appendix Table A includes lifetime one-county residents from all counties of five northwestern states: Idaho, Montana, Oregon, Washington and Wyoming; appendix Table B, from all counties of eight eastcentral states in the center of the Histoplasma area: Arkansas, Illinois, Indiana, Kentucky, Mississippi, Missouri, Ohio and Tennessee; and appendix Table C, from all counties of Arizona and New Mexico, and selected counties in California and Texas shown in Figure 1 as having frequencies of coccidioidin reactors of 5 per cent or more. (Recruits from low as well as high prevalence areas in the southwest have been included in order to increase the number of observations.)

As shown in Table II, derived from the three appendix tables, very few of the 5248 recruits from the five northwestern states reacted to either coccidioidin or histoplasmin. Most of those who had a positive reaction—an induration of 5 mm. or more—reacted only to one or the other antigen; only 3 persons reacted to both. It is apparent, therefore, that the material from the northwest can contribute little to the study of either specific or nonspecific reactions, but it should be useful for defining the characteristics of reactions in an uninfected (negative) population.

Among the 11,717 recruits from the eastcentral area, nearly two-thirds reacted to histoplasmin. Only a few reacted to coccidioidin, and most of them reacted also to histoplasmin, suggesting the expected association between reactions to the two antigens. It may also be noted that the frequency of persons who reacted to coccidioidin but not to histoplasmin was about as low as observed among recruits from the northwest.

The picture is quite different for recruits from the southwest. About 11 per cent (6.8 plus 4.3) reacted to coccidioidin, 8.2 per cent to histoplasmin and 4.3 per cent to both. Thus in the area endemic for coccidioidal infection, a high proportion of persons reacting to coccidioidin also react to histoplasmin—a finding in conformity with the accumulated evidence that nonspecific histoplasmin reactions are common among coccidioidin reactors. The fact that 3.9 per cent of recruits from this locality reacted to histoplasmin but not to coccidioidin is unexpected. Taken at its face value, this finding would seem to suggest the natural existence of *H. capsulatum* in the southwest, which is not in accord with the common belief

TABLE II

REACTIONS TO COCCIDIOIDIN (C) AND HISTOPLASMIN (H) AMONG NAVY RECRUITS, ACCORDING TO GEOGRAPHIC AREA OF LIFETIME RESIDENCE

	Northwest		Eastcentral		Southwest	
Reactor Group*	Number	Per Cent	Number	Per Cent	Number	Per Cent
C + H —	25	0.5	38	0.3	405	6.8
C + H +	3	0.1	143	1.2	256	4.3
C — H —	5,177	98.6	4,327	36.9	5,060	85.0
C — H +	43	0.8	7,209	61.6	232	3.9
Total tested	5,248	100.0	11,717	100.0	5,953	100.0

*+ = induration of 5 mm. or more.
— = induration of less than 5 mm.

that the two endemic areas are mutually exclusive.[31] Another possibility of course is that at least some of the histoplasmin reactions among coccidioidin non-reactors represent nonspecific reactions owing to infection with some fungus other than *C. immitis* or *H. capsulatum*.

Except for the histoplasmin reactions among coccidioidin non-reactors from the southwest, the results summarized in Table II are consistent with observations of other workers, based on a simple positive-negative classification with 5 mm. as the criterion. Further information can, however, be obtained by more detailed analysis of the present material.

Coccidioidin and Histoplasmin Sensitivity in the Northwest

Frequency histograms by size of reactions to coccidioidin and to histoplasmin for recruits from the northwest are given in Figure 3. Each column represents the percentage of the total group with reactions of a given size, ranging from 0 (no palpable induration) to more than 24 millimeters. Smooth-line curves have been superimposed (free-hand) on each histogram to bring out the pattern of response by compensating for obvious reading errors (excessive frequencies of reactions on "round" numbers and too few on some uneven numbers).

As shown in both sections of the figure, the great bulk of reactions are concentrated at the left end of the scale, forming a distinct group ranging from 0 to about 6 mm., with the highest frequency on 0 followed by rapidly decreasing frequencies. A second, very small group of reactions appears to center around 11 mm. The left-hand group in each distribution may be interpreted as representing the negative group, the presumably uninfected; whereas the right-hand group represents the few infected persons in an essentially negative population.

When, as in this instance, a very high proportion of the total group is uninfected, it would appear from the form of the distribution that negative reactions include most, if not all, of those measuring 5 and 6 mm.; and that the point of best separation between negatives and positives would be at about 7 mm. rather than at 5 mm. (It is not unreasonable to interpret 5 and 6 mm. reactions as negative, as reactions as large or even larger are occasionally found after intradermal injection of just saline or buffer diluent alone.[32, 33]) With 7 mm. instead of 5 mm. as the criterion, the percentage of reactors to coccidioidin among recruits from the northwest is 0.30 rather than 0.53; of positive histoplasmin reactors 0.55 rather than 0.88. Thus, even though the frequencies are extremely low, the 5 mm. criterion would over-estimate the percentage of Coccidioides-infected persons by some 76 per cent and the percentage of Histoplasma-infected by 60 per cent.

The presence of a few infected persons among lifetime residents of the northwest may reflect the existence of small, localized foci of Coccidioides and Histoplasma in some parts of that area; but more probably it is a result of deficiencies (or errors) in our residence classification. Periods of less than six months away from the home county were disregarded; hence a few persons may have spent short periods in the southwest or east-central area and acquired an infection with Coccidioides or Histoplasma.

Moreover, the higher frequency of histoplasmin than coccidioidin reactors may reflect a greater number of short trips into the geographically larger histoplasmal endemic area than into the more restricted coccidioidal endemic area.

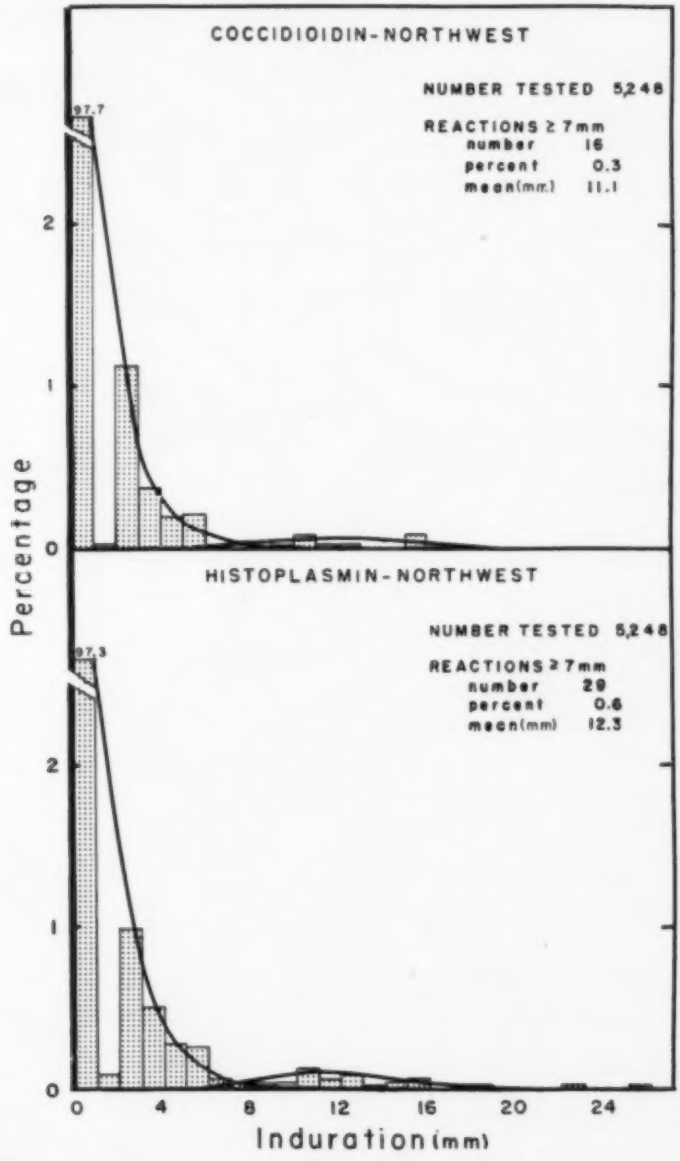

FIGURE 3: Frequency histograms of sizes of reactions to coccidioidin and to histoplasmin in Navy recruits from five northwestern states.

APPENDIX TABLE A. CORRELATION OF SIZES OF REACTIONS TO COCCIDIOIDIN AND TO HISTOPLASMIN AMONG 5,248 NAVY RECRUITS CLASSIFIED AS LIFETIME RESIDENTS OF FIVE NORTHWESTERN STATES

REACTION TO COCCIDIOIDIN in millimeters of induration	REACTION TO HISTOPLASMIN in millimeters of induration																											
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26+	Total
0	5,004	4	48	19	12	12	3	1	2	2	6	2	4	1	2	3	....	1	1	....	....	....	1	....	....	1	....	5,129
1	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1
2	52	....	1	3	3	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	60
3	18	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	19
4	9	....	....	2	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	11
5	10	....	2	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	12
6	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
7	2	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	2
8	1	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	2
9	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1
10	3	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	4
11	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1
12	....	....	....	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1
13	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
14	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
15	3	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	4
16	....	....	....	....	....	....	....	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1
Total	5,105	4	52	26	15	14	3	2	2	2	6	3	4	1	2	3	....	1	1	....	....	....	1	....	....	1	....	5,248

APPENDIX TABLE B. CORRELATION OF SIZES OF REACTIONS TO COCCIDIOIDIN AND HISTOPLASMIN AMONG 11,717 NAVY RECRUITS CLASSIFIED AS LIFETIME RESIDENTS OF EIGHT EAST-CENTRAL STATES

REACTION TO COCCIDIOIDIN in millimeters of induration	REACTION TO HISTOPLASMIN in millimeters of induration																											
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	+Total
0	3,690	1	228	140	209	406	428	569	780	540	1,568	396	699	243	277	550	53	87	79	18	161	6	25	8	6	21	16	11,204
1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
2	29	....	5	1	7	4	7	8	6	13	32	14	14	7	9	17	....	2	5	....	4	....	1	....	....	....	1	186
3	9	....	1	....	2	3	....	8	8	6	19	7	12	6	3	10	3	1	1	1	6	....	1	....	....	....	....	107
4	4	....	1	....	....	....	1	1	2	1	9	1	5	2	5	2	....	2	....	....	2	....	....	....	....	....	1	39
5	6	....	....	....	....	3	....	4	2	3	11	8	4	9	4	8	1	3	1	1	2	....	1	....	....	....	....	71
6	6	....	1	....	....	5	....	....	2	1	3	....	1	1	2	....	....	....	....	....	1	....	....	....	....	....	....	23
7	3	....	....	1	1	....	....	1	1	....	5	1	1	....	....	....	....	....	....	....	2	....	....	....	....	1	....	17
8	2	....	....	....	....	....	2	....	3	1	5	1	1	2	1	1	....	....	....	....	....	....	....	....	1	....	....	20
9	5	....	....	....	....	....	....	....	1	1	....	1	....	....	2	1	....	....	....	....	1	....	....	....	....	....	....	12
10	5	....	1	....	....	2	....	....	1	1	....	....	1	1	1	4	....	....	....	....	3	....	....	....	....	....	....	20
11	3	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	4
12	....	....	....	....	....	1	....	....	....	1	1	1	....	....	1	....	1	....	....	....	....	....	....	....	....	....	....	6
13	1	....	....	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	2
14	1	....	....	....	....	....	....	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	2
15	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1	....	1
16	1	....	....	....	....	1	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	3
Total	3,765	1	238	142	219	425	438	592	806	568	1,654	431	738	271	305	593	58	95	86	20	182	6	28	8	7	23	18	11,717

APPENDIX TABLE C. CORRELATION OF SIZES OF REACTIONS TO COCCIDIOIDIN AND HISTOPLASMIN AMONG 5,953 NAVY RECRUITS CLASSIFIED AS LIFETIME RESIDENTS OF FOUR SOUTHWESTERN STATES

REACTION TO COCCIDIOIDIN in millimeters of induration	REACTION TO HISTOPLASMIN in millimeters of induration																										
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26+	Total
0	4,785	....	99	38	21	26	23	30	30	16	41	10	13	2	5	13	1	2	2	....	....	....	....	....	....	....	1	5,158
1	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1
2	55	....	6	6	2	1	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	71
3	22	....	4	2	2	2	1	....	....	....	1	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	35
4	13	....	....	1	3	1	....	4	1	1	2	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	27
5	28	....	5	1	....	5	2	1	1	....	3	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	46
6	16	....	6	2	1	2	2	1	3	....	3	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	37
7	29	....	8	2	....	7	2	....	1	....	2	....	....	....	....	1	....	....	....	....	1	....	....	....	....	....	....	53
8	46	....	4	1	2	3	2	2	....	....	5	....	1	....	....	1	....	....	....	....	....	....	....	....	....	....	....	67
9	26	....	5	1	4	9	2	2	2	2	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	53
10	62	....	5	4	4	15	4	7	7	4	4	....	1	1	....	2	....	....	....	....	1	....	....	....	....	....	....	121
11	12	....	4	3	1	3	1	3	1	....	....	....	2	....	....	....	....	....	....	....	....	....	....	....	....	....	....	30
12	20	....	6	2	4	6	7	3	8	3	5	....	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	65
13	11	....	....	....	2	....	4	2	2	1	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	23
14	6	....	2	2	3	1	1	1	2	3	2	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	23
15	20	....	3	1	3	17	....	4	5	2	8	....	2	....	....	....	....	....	....	....	....	....	....	....	....	....	....	65
16	2	....	1	....	1	....	3	1	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	9
17	2	....	....	....	....	2	....	2	1	1	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	9
18	6	....	1	2	....	....	....	3	1	1	1	2	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	18
19	1	....	1	....	....	....	....	....	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	3
20	9	....	3	....	....	4	1	3	1	1	2	....	....	1	....	1	....	....	....	....	....	....	....	....	....	....	....	26
21	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	1
22	1	....	1	....	....	....	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	3
23	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
24	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....
25	1	....	....	....	....	....	....	....	1	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	3
26	5	....	....	....	....	1	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	....	6
Total	5,179	....	165	68	53	105	55	70	68	35	82	12	25	4	5	18	2	2	2	....	2	....	....	....	....	....	1	5,953

Coccidioidin Sensitivity in the Southwestern and Histoplasmin Sensitivity in the Eastcentral States

Frequency histograms are given in the upper section of Figure 4 for reactions to coccidioidin among residents of the southwest and in the lower section for reactions to histoplasmin among residents of the eastcentral states. (Note that the vertical scale is not the same for the two distributions.) Both histograms, like those for the northwest, show a bimodal pattern reflecting the presence in each population of two groups. One group, which may be interpreted as negative or uninfected, has a high frequency of reactions at 0 mm. Reactions of the other group—the positive, presumably infected—are distributed in a form resembling the normal probability frequency curve with a peak around 11 mm. As indicated by the free-hand, smooth-line curves, the two groups overlap one another to some degree.

The two histograms in Figure 4 differ strikingly from one another, and also from those for the northwest, in the proportion of reactions falling into the positive group. Coccidioidin sensitivity in the southwest is many times more prevalent than in the northwest; and reactions in the positive group spread over a broader range to include not only the 6 mm. reactions but most of the 5 and some of the 4 mm. reactions. With the much higher prevalence of sensitivity to histoplasmin in the eastcentral area, the positive histoplasmin reactions appear to cover an even broader range to include most of the 4 and some of the 3 mm. reactions. Yet because of the overlapping of the positive and negative distributions, the smaller positive reactions cannot be distinguished from the larger negative reactions. Thus, reactions of 3, 4 and 5 mm., at least, have to be interpreted in the individual case as doubtful, meaning that they may belong to either the positive or negative group.

According to the form of the distributions, the generally accepted 5 mm. criterion would probably give the best separation of coccidioidal infected and uninfected in the southwest, while a criterion of 4 mm. would appear to be more effective for separating histoplasmal infected from uninfected in the eastcentral area.

It is obvious that the position of the positive group on the size scale and, consequently, the point of separation between positives and negatives, depends on the potency or concentration of the particular antigen used for testing. In the present instance, a slightly higher concentration of both coccidioidin and histoplasmin could be expected to shift the positive distribution a few millimeters farther to the right and thereby effect a more clean-cut separation between the positive and negative groups by reducing the frequencies of reactions in the doubtful range. As will be evident later, however, an increase in dosage would probably not help to separate specific from the non-specific reactions that are prevalent in some localities.

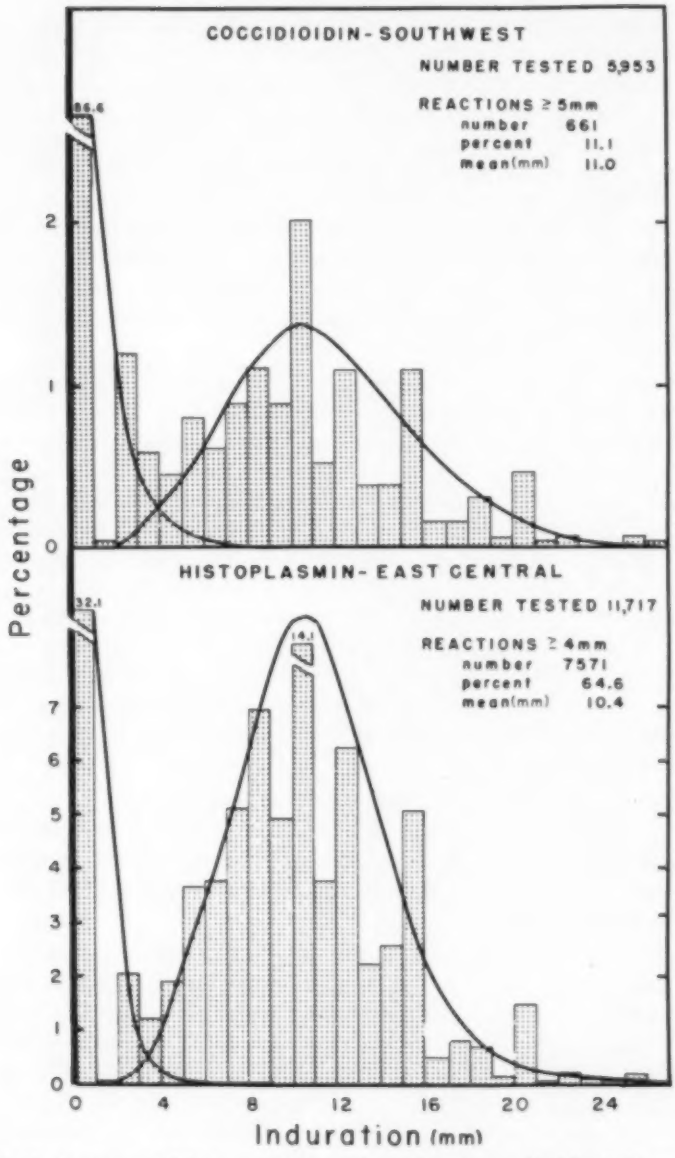

FIGURE 4: Frequency histograms of sizes of reactions to coccidioidin in Navy recruits from four southeastern states and to histoplasmin in Navy recruits from eight east-central states.

*Relation Between Size and Prevalence of Reactions in the Endemic Area**

Before examining the characteristics of coccidioidin reactions in the histoplasmal endemic area and histoplasmin reactions in the coccidioidal endemic area, it is pertinent to consider whether the sizes of reactions to coccidioidin and to histoplasmin vary with the prevalence of infection in the respective endemic areas. For example, repeated infection with a particular fungus is more likely to occur in persons living all their lives in an area with a high rather than a low prevalence of infection with that fungus. If, as some workers have suggested, repeated infection is necessary to prevent a loss or waning of sensitivity, or if repeated infection acts as a "booster" to increase the degree of sensitivity, reactions could then be expected to be larger in high prevalence areas and smaller in low prevalence areas.

To investigate the question, results of coccidioidin tests were tabulated separately for lifetime residents of selected areas in the southwest with different prevalences of coccidioidin sensitivity. The results are illustrated in the upper section of Figure 5 by three frequency curves, one representing the distribution of reactions for recruits from areas with a low prevalence, averaging about 7 per cent; another with prevalences averaging nearly 29 per cent; and a third averaging about 45 per cent. The points for each curve represent 3-point moving averages plotted at 2 mm. intervals.

From the material presented in Figure 5, it is seen that the distributions of reactions comprising the positive segment of each population have essentially the same form and center at about the same place on the scale, regardless of the frequency of reactors. The mean size of reactions 5 mm. or more in the three distributions differs by only half a millimeter: 10.6, 11.1 and 10.7 mm. Yet more persons in the high prevalence areas have undoubtedly been infected repeatedly and possibly with larger infecting doses than in the low prevalence areas; those factors, and perhaps others, apparently affect only the prevalence but not the degree of coccidioidin sensitivity.

The lower section of Figure 5 shows the results for a similar analysis of histoplasmin reactions among lifetime residents of selected areas in the eastcentral part of the country. The frequency of positive reactors in the low prevalence area averaged 11.7 per cent, in the intermediate prevalence area 42.2 per cent and in the high prevalence area 76.9 per cent. Despite the wide differences in prevalence, the distributions of positive reactions have about the same form and center at about the same place on the scale. Moreover, the mean sizes of reactions 4 mm. or more are remarkably alike: 10.4, 10.8 and 10.3 mm. The degree of sensitivity to histoplasmin in the Histoplasma endemic area, as to coccidioidin in the Coccidioides endemic area, is apparently not affected by the prevalence of infection.

*This section includes results for student nurses and college students as well as Navy recruits.

Coccidioidin Sensitivity in the Eastcentral Area and Histoplasmin Sensitivity in the Southwest

Coccidioidin reactions among the nearly 12,000 Navy recruits from the Histoplasma endemic area (eastcentral) and histoplasmin reactions among the 6,000 recruits from the Coccidioides endemic area (southwest) are shown as frequency histograms in Figure 6. Both histograms appear to be unimodal—one-peaked—with high frequencies at 0 mm. followed by

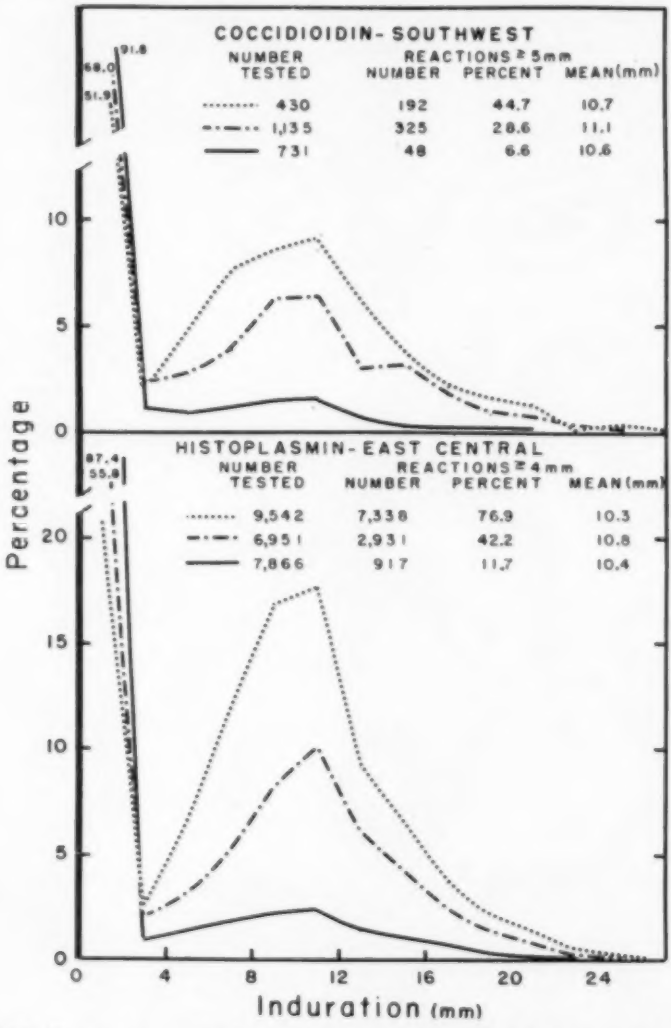

FIGURE 5: Frequency curves of sizes of reactions to coccidioidin in young adults from three southwestern localities with different prevalences of coccidioidin sensitivity and to histoplasmin from three eastcentral localities with different prevalences of histoplasmin sensitivity.

progressively lower frequencies. In some respects the form of both histograms resembles those from the northwest, but with relatively many more small and moderate sized reactions. Although a group of positive (specific) reactions and a group of negative reactions cannot be distin-

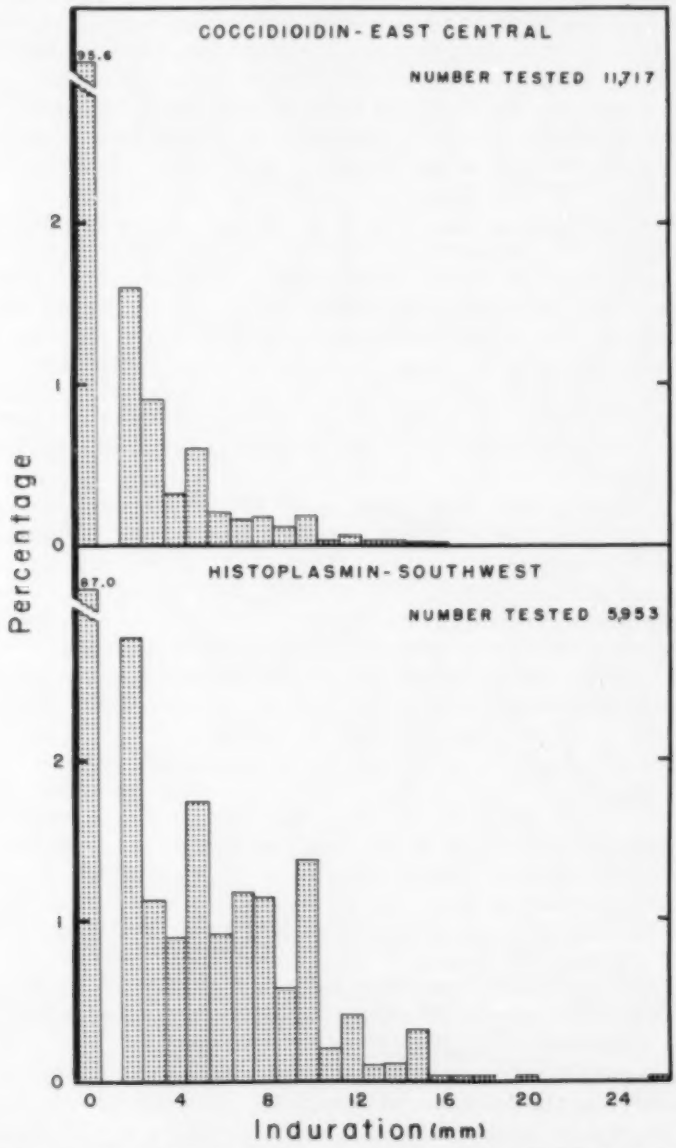

FIGURE 6: Frequency histograms of sizes of reactions to coccidioidin in Navy recruits from eight eastcentral states and to histoplasmin in Navy recruits from four southwestern states.

guished in either histogram, it must be assumed that both are present. Thus, most of the reactions larger than about 12 mm. undoubtedly represent the right hand end of a positive group similar to those seen in Figure 3. And a group of negative reactions ranging from 0 to 5 or 6 mm. must also be present in each distribution. The bulk of reactions concentrated in the potential interval between those two groups are assumed to represent a third group—one we should interpret as neither positive nor negative but as nonspecific. Reactions in that third group apparently average around 7 mm. and range in size from 2 to about 10 or 12 mm. It is evident, too, that the frequency of nonspecific reactions to histoplasmin in the southwest is much greater than the frequency of nonspecific reactions to coccidioidin in the eastcentral area.

Further analysis of the data is given in Figure 7. (Note that the vertical scale differs in the two sections of the figure). The upper section of the figure shows frequency curves of coccidioidin reactions for the 11,717 recruits from the eastcentral area, subdivided into three groups. One subgroup consists of men with histoplasmin reactions of 0 to 3 mm., the second with histoplasmin reactions of 4 to 10 mm., and the third with histoplasmin reactions of 11 mm. or more. The points for each curve represent 3-point moving averages plotted at 2 mm. intervals. The three curves together represent a breakdown of the distribution shown in the upper section of Figure 6.

Among recruits with clearly negative (0-3 mm.) reactions to histoplasmin, 1.3 per cent had coccidioidin reactions of 3 mm. or more. The frequency of coccidioidin reactions increased to 2.7 per cent for persons with histoplasmin reactions of 4-10 mm. and to 5.2 per cent for those with histoplasmin reactions of 11 mm. or more. The mean size of coccidioidin reactions measuring 3 mm. or more among negative histoplasmin reactors was 6.9 mm. The coccidioidin reactions were smaller, however, in recruits sensitive to histoplasmin: the mean size was just over 5 mm. for persons with either small or large histoplasmin reactions.

The lower section of Figure 7 gives a corresponding analysis of histoplasmin reactions for the nearly 6,000 recruits from the southwest, subdivided into three groups by the size of their coccidioidin reactions. There was a pronounced increase in frequency of histoplasmin reactions with increase in degree of coccidioidin sensitivity. The percentage of histoplasmin reactions 3 mm. or more was 5.6 for persons with coccidioidin reactions of 0-3 mm., 37.4 per cent for those with small coccidioidin reactions and 58.1 per cent for those with large coccidioidin reactions. The mean size of the histoplasmin reactions measuring 3 mm. or more was 7.6 mm. in clearly negative coccidioidin reactors and slightly smaller, close to 7 mm., in those with either small or large coccidioidin reactions.

These results are in agreement with the observation of Smith and his associates[29] that the frequency of nonspecific reactions increases with the size of the specific reactions. But our results do not agree with theirs that the *size* of nonspecific reactions also increases with the size of specific reactions. This descrepancy may be related to the fact that Smith's analysis

was based on the study of two groups, one referred to as "dominant" reactors to histoplasmin and the other as "dominant" reactors to coccidioidin; whereas our material was grouped according to geographic locality of life-

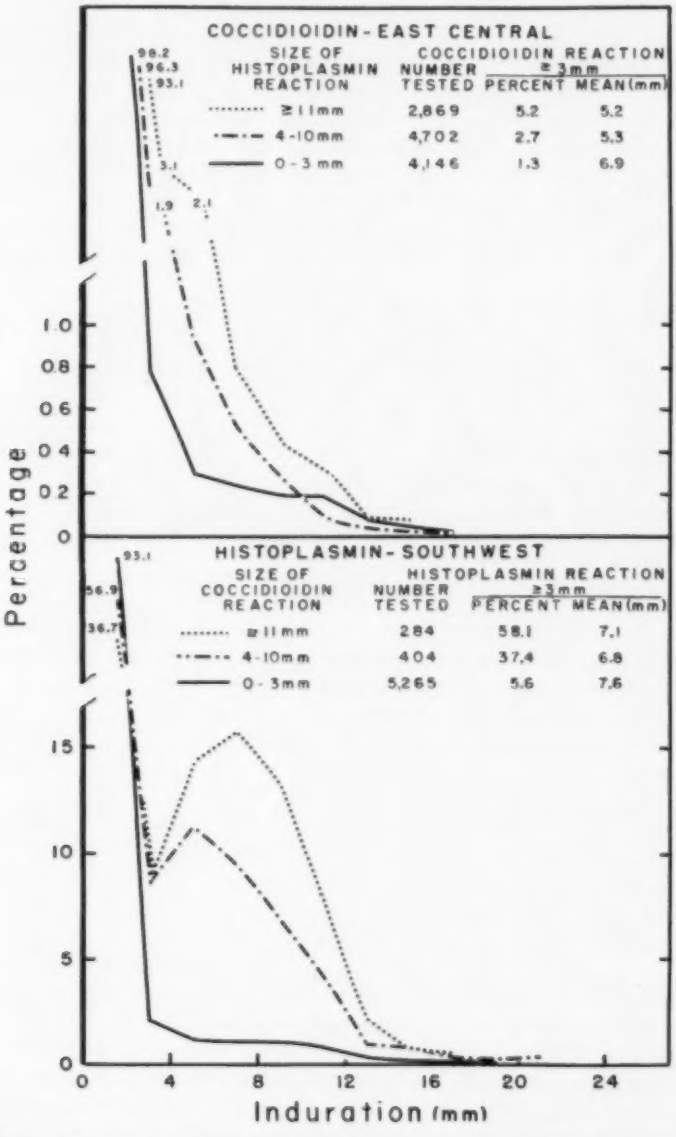

FIGURE 7: Frequency curves of sizes of reactions to coccidioidin in Navy recruits from four southwestern states, subdivided into three groups by size of histoplasmin reaction; and to histoplasmin in Navy recruits from eight eastcentral states, subdivided into three groups by size of coccidioidin reaction.

time residence, regardless of "dominant" sensitivity. Even if our material were adjusted by excluding "dominant" histoplasmin reactors from the southwestern population and "dominant" coccidioidin reactors from the eastcentral population, we could not demonstrate an appreciable increase in size of nonspecific reactions with increase in size of presumably specific reactions. While the point at issue may not be of immediate practical importance, it bears directly on the nature of specific and nonspecific sensitivity. Thus Smith's result would seem to suggest that the heterologous antigen acts like a more dilute concentration of the homologous antigen, and that the relation between dose of antigen and size of reaction (the dose-response curve) is similar for specific and nonspecific sensitivity. Our results are more in line with what might be expected if the homologous and heterologous antigens were qualitatively different and that the dose-response curve is fundamentally different for specific and nonspecific sensitivity.

Our results are also not in accord with the common impression that an individual who reacts "positively" to one fungus antigen usually will react to another fungus antigen. Our material shows that although many lifetime residents of the southwest with large reactions to coccidioidin also react to histoplasmin, many others do not react to histoplasmin. One might therefore speculate on the possibility that some persons lack the capacity to react nonspecifically; moreover, such persons may differ in some important biological, perhaps immunological characteristic from those who do react nonspecifically. The matter would seem to be worth looking into.

Discussion

From this and other reports, it is evident that the nature of specific and nonspecific sensitivity is complex and our understanding of it still rudimentary. As many unanswered questions need further study, we should like only to comment briefly on some of the present results.

We believe, and have tried to show, that the traditional positive-negative classification of skin reactions, based on a fixed point of separation at 5 mm., has serious limitations. The term "positive" is generally used to mean "specific"; yet it is well known that some reactions exceeding 5 mm. in size may be nonspecific, some may in fact be negative. Thus it would seem desirable, particularly for research work, to express skin testing results as frequency distributions of carefully measured sizes of reactions.

The initial purpose of the present study was to obtain material on the variations in prevalence of sensitivity to coccidioidin, histoplasmin and tuberculin, and results of tests with the two fungus antigens are presented in conventional terms in the two maps, Figures 1 and 2. The maps show variations in the prevalence of reactions of 5 mm. or more. From the more detailed analysis of the material, especially the frequency distributions of the sizes of reactions, it would appear that the prevalence of reactions measuring 5 mm. or more to histoplasmin in the eastcentral area and to coccidioidin in the southwestern area probably represent fair estimates of the prevalence of specific infection in young adults in those two

areas. But the histoplasmin reactions in the southwest and the coccidioidin reactions in the eastcentral area presumably represent mixtures of varying (and unknown) proportions of specific and nonspecific reactions.

In the eastcentral area, relatively few lifetime residents react to coccidioidin. Most of the coccidioidin reactions are small and are found in persons who also react to histoplasmin, suggesting that they are cross-reactions owing to infection with Histoplasma. Very few lifetime residents of the eastcentral states react to coccidioidin but not to histoplasmin. Some of them have the large reactions characteristic of the presumably specific coccidioidin reactions found in the southwest: such reactions most likely represent coccidioidal infection acquired outside of the Histoplasma endemic area. The remaining coccidioidin reactions among histoplasmin non-reactors are small and may represent nonspecific sensitization by some fungus other than Histoplasma.[34]

Interpretation of the relatively high frequency of histoplasmin reactions in lifetime residents of the southwest is somewhat more complex. It is apparent, first, that a rather high proportion are small reactions in persons sensitive to coccidioidin and that they probably represent cross-reactions owing to sensitization by coccidioidal infection. But many of the histoplamin reactions found in the southwest cannot be so interpreted. Most of the large reactions found in coccidioidin non-reactors must represent specific histoplasmin sensitivity—some acquired outside the coccidioidal endemic area, some perhaps acquired within that area. However, a substantial group of lifetime residents of the southwest do not react to coccidioidin but have small reactions to histoplasmin. It would seem reasonable to postulate that such reactions represent infection with some other fungus or fungi that cause cross-reactions with histoplasmin. Moreover, it would appear that the prevalence of infection with the other fungi may be about as high as the prevalence of coccidioidal infection, if the frequency of histoplasmin cross-reactions is the same in persons infected with the unidentified fungi as it is in persons infected with Coccidioides.

Some years ago Emmons and Ashburn[35] reported the isolation of *Haplosporangium parvum* from wild rodents in Arizona and sensitivity to haplosporangin among some of the school children in the area. A strong degree of cross-reaction was subsequently shown in experimental animals between haplosporangin, blastomycin and histoplasmin.[27] Howell[28] also demonstrated a strong cross-reaction between histoplasmin and blastomycin. Thus there would seem to be a number of different fungi that should be investigated as possible sources of the nonspecific sensitivity to histoplasmin found in the southwest.[29]

SUMMARY

More than 110,000 young adults—Navy recruits, college students and student nurses—from nearly all parts of the country were tested simultaneously with coccidioidin and histoplasmin between the years 1945 and 1951. Results for persons classified as lifetime residents of a single county provide material for mapping geographic variations in the prevalence

of coccidioidin and histoplasmin sensitivity, based on the conventional 5 mm. criterion for a positive reaction.

Correlations of reactions to coccidioidin and histoplasmin are studied in three groups of Navy recruits, lifetime residents of five northwestern states, of eight eastcentral states and of four southwestern states. Just over 1 per cent of recruits from the northwest reacted to either coccidioidin or histoplasmin. More than 60 per cent of recruits from the Histoplasma endemic area (eastcentral) reacted to histoplasmin, 1.5 per cent to coccidioidin and 1.2 per cent to both. Eleven per cent of those from the Coccidioides endemic area (southwest) reacted to coccidioidin, 8 per cent to histoplasmin and just over 4 per cent reacted to both antigens.

Reactions to the homologous antigen in the endemic area—presumably specific reactions—were appreciably larger, on the average, than reactions in the non-endemic areas. Moreover, as the mean size of specific reactions does not appear to vary with variations in the prevalence of sensitivity, the smaller reactions found in the non-endemic areas are interpreted as nonspecific. Relatively few of the small, presumably nonspecific reactions to coccidioidin were found in lifetime residents of the eastcentral area, and most of them were probably cross-reactions with Histoplasma. Some of the presumably nonspecific reactions to histoplasmin in the southwest can likewise be ascribed to cross-reactions with Coccidioides. But the substantial frequency of small histoplasmin reactions found in coccidioidin non-reactors probably represent infection with some other fungus, or fungi, which may be as prevalent as Coccidioides in the southwest.

The criterion for a positive (specific) reaction is shown to vary with the prevalence of both specific and nonspecific sensitivity. The use of the conventional 5 mm. criterion can therefore be misleading, as it overestimates the percentage of specific reactions in some localities and underestimates it in others. Careful measurement of the sizes of reactions, with detailed study of frequency distributions of the measured sizes, can provide much needed information on the complex and little understood nature of specific and nonspecific sensitivity.

RESUMEN

Más de 110.000 adultos jóvenes incluyendo reclutas marinos, estudiantes de secundaria y estudiantes de enfermería, de todas partes del País, se sometieron a las reacciones cutáneas de coccidioidina, e histoplasmina entre 1945 y 1951.

Los resultados entre personas clasificadas como residentes de toda la vida de un condado único proporcionan material para hacer el mapa de las incidencias geográficas variables de las dos micosis mencionadas basándose en el criterio de dimensiones de 5 mm. par las reacciones positivas.

La correlación de las reacciones a la coccidioidina e histoplasmina se estudian en tres grupos de reclutas marinos, residentes de toda la vida de cinco estados al noroeste, de ocho estados centrales, y de cuatro estados del sudeste. Más de uno por ciento de los reclutas del noroeste reaccionaron ya sea a la coccidioidino o a la histoplasmina. Más de 60 por ciento de los reclutas provinientes del área de endemia histoplásmica (este-central)

reaccionaron a la histoplasmina, 1.5 por ciento a la coccidioidina y 1.2 por ciento a ambas.

Once por ciento de los del área de coccidioides endémica (sudeste) reaccionaron a la coccidioidina, 8 por ciento a la histoplasmina y más de cuatro por ciento para ambos antígenos.

Las reacciones al antígeno homólogo en el área endémica-reacciones que se presumieron específicas-fueron notablemente mayores, por término medio, que las reacciones en las áreas no endémicas. Más aún, como el tamaño medio de las reacciones específicas no parece variar con la diversidad de prevalencia de la sensibilidad, las reacciones más pequeñas encontradas en las áreas no endémicas se interpretaron como no específicas. Relativamente pocas de las reacciones pequeñas que se estimaron como no específicas a la coccidioidina se encontraron entre los residentes de toda la vida del área este-central y la mayoría de ellas fueron probablemente reacciones cruzadas con el histoplasma.

Algunas de las reacciones que se consideraron no específicas a la histoplasmin en la región del sudoeste pueden del mismo modo ser atribuídas a reacciones cruzadas con coccidioides.

Pero la frecuencia de pequeñas reacciones a la histoplasmina entre no reactores a la coccidioidina deben representar la infección por otros hongos que pueden ser tan prevalecientes como la coccidioides en el sudoeste.

El criterio para considerar positiva (específica) una reacciónse ve que varía con la prevalencia de las sensibilidades tanto específica como no específica. El uso de la medida generalmente aceptada de 5 mm. puede por tanto ser motivo de error puesto que sobrestima el porcentaje de reacciones no específicas en algunas localidades y la subestima en otras.

La medida cuidadosa del tamaño de las reacciones con detalle de la frecuencia de distribución de los tamaños medidos pueden dar una información muy necesaria sobre la naturaleza compleja y poco comprendida de las sensibilidades específica y no específica.

RESUME

Les auteurs ont recherché simultanément les réactions à la coccidioidomycine et à l'histoplasmine, chez plus de 100.000 jeunes adultes (recrues de la Marine, étudiants des Universités, jeunes filles faisant leurs études d'infirmières) provenant de presque toutes les régions, entre 1945 et 1951. Les résultats concernant les personnes résidant en permanence dans une seule région ont permis d'établir le plan des variations géographiques de la fréquence de la sensibilité à la coccidioidomycine et à l'histoplasmine. On s'est basé pour cela sur le critère conventionnel d'une réaction considérée comme positive à partir de 5 mm.

Les rapports entre les réactions à la coccidioidomycine et à l'histoplasmine one été étudiées pour les recrues de la Marine, en les répartissant en trois groupes: résidents permanents de cinq états du Nord-Quest, de huit états du Centre-est, et de quatre états du Sud-ouest. A peine plus d'un pour cent des recrues du Nord-ouest réagirent, soit à la coccidioido-

mycine, soit à l'histoplasmine. Plus de 60% des recrues réagirent à l'histoplasmine, dans la région où l'histoplasmose se trouve à l'état endémique (centre-est), 1,5% réagirent à la coccidioidomycine, et 1,2% aux deux à la fois. 11% de ceux qui venaient de la région endémique du Sud-ouest réagirent à la coccidioidomycine, 8% à l'histoplasmine, et à peine plus de 4% réagirent aux deux antigènes.

Les réactions à l'antigène de l'affection existant dans la région à l'état endémique (réactions vraisemblablement spécifiques) furent considérablement plus importantes en moyenne que les réactions là où l'affection n'existait pas à l'état endémique. En outre, comme la moyenne de l'importance des réactions spécifiques ne semble pas varier en fonction du degré de la sensibilité, les réactions discrètes constatées dans les régions non-endémiques n'ont pas été considérées comme spécifiques. Chez les résidents permanents de la région centre-est le nombre des réactions discrètes à la coccidioidomycine tenues pour non spécifiques se montra relativement peu important. La plupart d'entre elles correspondaient probablement à des réactions croisées avec l'histoplasmine. Certaines réactions à l'histoplasmine, considérées comme non-spécifiques, peuvent de même interprétées comme des réactions croisées à la coccidioidomycine chez les individus venant du Sud-ouest. Mais la fréquence notable des réactions faibles à l'histoplasmine, constatées chez les individus ne réagissant pas à la coccidioidomycine doit évoquer l'existence d'une infection provenant de quel que autre champignon, qui se rencontrerait d'une façon aussi importante que la coccidioidomycose dans le sud-ouest.

Le critère selon lequel on détermine si une réaction spécifique est positive varie selon la prévalence de la sensibilité tant spécifique que non-spécifique. L'emploi du critère conventionnel de 5 mm. peut donc être trompeur, il peut faire surestimer le pourcentage des réactions non-spécifiques dans certaines localités, et la faire sous-estimer dans d'autres.

Une mensuration soigneuse des dimensions des réactions, avec étude détaillée de leurs variations peut fournir beaucoup d'indications précieuses sur la nature complexe et encore mal comprise de la sensibilité spécifique et non-spécifique.

ZUSAMMENFASSUNG

Es wurden mehr als 110.000 jugendliche Erwachsene-Marineanwärter, Hochschulstudenten und Schwesternschülerinnen-aus nahezu allen Teilen der USA gleichzeitig mit Coccidioidin un Histoplasmin getestet in dem Zeitraum der Jahre zwischen 1945 und 1951. Die Ergebnisse in ihrer Klassifizierung für Personen als Lebenslange Bewohner ein und desselben Kreises gewährleisten ein Material zur cartographischen Darstellung der geographischen Variationen im Auftreten der Empfindlichkeit gegen Coccidioidin und Histoplasmin, ausgehend von dem konventionellen 5 mm-Mass für eine positive Reaktion.

Einer Untersuchung unterzogen wurden die Beziehungen zwischen den Reaktionen auf Coccidioidin und auf Histoplasmin in 3 Gruppen von Marineanwärtern, lebenslangen Einwohnern von 5 Staaten des Nordwestens der USA, 8 östlichen Zentralstaaten und 4 Südweststaaten. Gerade

eben mehr als 1% der Anwärter aus dem Nordwesten reagierten entweder auf Coccidiodin oder auf Histoplasmin. Mehr als 60% der Anwärter aus dem für Histoplasma endemischen Gebiet (östliche Zentralstaaten) reagierte auf Histoplasmin, 1,5% auf Coccidiodin und 1,2% auf beide. 11% derjenigen aus dem für Coccidioides endemischen Gebiet (Südweststaaten) reagierten auf Coccidioidin, 8% auf Histoplasmin und eben mehr als 4% reagierten auf beide Antigene.

Reaktionen auf das Homologe Antigen im endemischen Gebiet-vermutlich spezifische Reaktionen-waren beträchtlich grösser im Durchschnitt als Reaktionen in den nicht endemischen Bereichen. Darüber hinaus werden, da die mittlere Grösse der spezifischen Reaktionen nicht zu schwanken scheint, mit Schwankungen im Auftreten der Empfindlichkeit die in den nicht endemischen Gebieten gefundenen geringeren Reaktionen als unspezifisch gedeutet. Relativ wenige der geringen, vermutlich unspezifischen Reaktionen auf Coccidioidin fanden sich bei den lebenslangen Einwohnern der östlichen Zentralstaaten und die meisten von ihnen waren wahrscheinlich gekreuzte Reaktionen mit Histoplasma. Manche der vermutlich unspezifischen Reaktionen auf Histoplasmin im Südwesten können in gleicher Weise gekreuzten Reaktionen mit Coccidioides zugeschrieben werden. Die beträchtliche Häufigkeit jedoch von kleinen Histoplasmin-Reaktionen, die sich unter den nicht auf Coccioidin reagierenden Personen fanden, müssen Infektionen mit irgend einem anderen Pilz bedeuten, oder mit mehreren Pilzen, die ebenso häufig zu sin scheinen wie Coccidioides im Südwesten.

Es wird gezeigt, dass der Masstab für eine positive (spezifische) Reaktion schwankt mit dem Auftreten sowohl der spezifischen als auch der nichtspezifischen Empfindlichkeit. Die Anwendung des konventionellen 5mm-Masses kann daher in die Irre führen, weil es den Prozentsatz nichtspezifischer Reaktionen in manchen Gegenden überschätzt und ihn in anderen unterschätzt.

Sorgfältige Messung der Grösse der Reaktionen mit ins einzelne gehenden Untersuchungen der Häufigkeitsverteilung der gemessenen Grössen kann zur Beibringung von vielen der noch notwendigen Unterlagen über die complexe und wenig geklärte Natur der spezifischen und unspezifischen Sensibilität beitragen.

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Myxoma Cordis

Diagnosis Established Pre-operatively; Surgical Removal of the Tumour

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Myxoma cordis is a rare disorder. Up to 1951, 128 cases were known in the literature (Mahaim, Prichart). It has long been a subject of controversy whether these formations were to be regarded as organized thrombi or as tumours, but now they are considered as tumours. The myxomas are the most frequently occurring primary tumours of the heart, viz., about 50 per cent. In 50 per cent of cases they are polypous neoplasms of a partly gelatinous, partly rubber-like consistency, as a rule with a pedicle, arising from the auricular septum close to the foramen ovale. In 75 per cent they are situated in the left atrium. They have been observed in all age-groups in both sexes, but mainly between the 30th and 60th year of life. The size may vary from a pea to that of a closed fist. The small tumours cause no symptom.

Before dealing with clinical symptoms of the larger-sized tumours, we will first report the case-history of a patient examined by us.

J. K. R., male, age 45. One year previous to the time of writing he suffered from palpitations and an oppressed feeling in the chest when cycling against the wind. These symptoms disappeared as soon as he rested. The complaints increased gradually, especially in the last eight months. When he had been in a stooping position and then straightened himself, he became dizzy and felt palpitations, lasting for some hours. During the last six months he became short-winded if he had only walked about 25 metres, or on slight exertion. Stooping made him short of breath, which improved as soon as he stood up again. He was also unable to sleep on his right side as he used to do, for then again he became dyspnoeic. He was however able to sleep well when lying on his back or on the left side, but his head had to be elevated. Of late coughing had become worse, with sensations of vertigo. During the last year he had repeatedly suffered from attacks of bronchitis, sometimes also from fever. His appetite was good, micturition and defaecation were normal. He had not had swollen feet. In his youth he had often suffered from bronchitis with attacks of wheezing, lasting for about one week. There was no history of rheumatic affections.

He was a normally built man, in good nutritional condition, without cyanosis or oedema. Pulse: regular, equal, rate 88/min. Respiration: 18/min. Blood pressure: 130/90. The venous pressure was not increased.

The apex beat was not palpable. Percussion showed the heart to extend from the midclavicular-line to the mid-line. The first sound at the apex was not loud, but split; the second pulmonary sound was accentuated. There was no murmur, in the supine or in the lateral position. Percussion was normal over the lungs; the pulmonary boundaries did not show large excursions; expiration was prolonged, with wheezing rales.

Liver and spleen were not palpable. Urine: albumen negative; glucose negative; urobilin trace; sedimentation normal. Haemoglobin content 80 per cent; erythrocytes 4,400,000; leucocytes 8,100; eosinophils 3 per cent, polynuclears 68 per cent, lymphocytes 24 per cent, monocytes 5 per cent. Erythrocyte sedimentation rate 19 mm. after one hour.

X-ray film of the thorax (Fig. 1): The heart was not enlarged, marked hilar shadows radiating towards the periphery, no hilar pulsations. In the right oblique position an impression of the oesophagus near the left atrium was visible (Fig. 2). On fluoroscopy the extremely strong pulsatory movements of the oesophagus at the

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FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Posterior-anterior x-ray (J. K. R.).—*Figure 2:* Right oblique position; slight impression on esophagus.—*Figure 3:* Kymogram of esophagus.

level of the left auriculum formed a striking feature. The kymogram revealed (Fig. 3) that these pulsations coincided with ventricular systole.

ECG (Fig. 4): sinus rhythm PR 0.2 seconds, QRS 0.08 seconds, high P-peaks in II, III, AVF, negative P in V_1, diphasic P in V_2 and V_3, right hypertrophy (QR in AVR, negative T in III, V_1-V_3, R, in V_5 and V_6).

Circulation time 13 seconds (magnesium sulphate). Vital capacity 3,225 ml. (normal value 4,110 ml.), residual air 36 per cent, functional residual air 58.5 per cent.

On cardiac catheterization the following values were found:

	O_2-Saturation Per Cent	Pressure	Mean Pressure
Right auricle	54	7 mm. Hg	
Right ventricle	53.5	120/0 mm. Hg	
Pulmonary artery trunk	49	120/50 mm. Hg	84 cm. H_2O
Pulmonary artery periphery	98.5	40 mm. Hg	47 cm. H_2O
Radial artery	96.5	130/90 mm. Hg	

The curve obtained from the periphery of the pulmonary artery (P.C.P. curve) showed a remarkably early start of the V-wave which was also extremely high (Fig. 5), and a missing X-dip, consequently a positive venous pulse.

The complete picture was highly reminiscent of mitral stenosis without murmurs with considerable pulmonary congestion. The high pressure in the pulmonary artery and right ventricle could likewise be explained in this way, but murmurs were never heard, and in the E.C.G. the right strain was indeed explicable. Angiocardiography, however, led to the solution.

This technique (Figs. 6a and 6b) revealed a slow passage of the contrast fluid throughout the pulmonary circulation (after eight seconds still in the pulmonary artery, after 12-14 seconds a well-filled left auricle was observed). *A gap was visible in the shadow of the left auricle. This made a tumor in the left auricle plausible, a myxoma being especially suggested.* The history and course of the disease also provided arguments in favour of this (see below). An operation was therefore considered. Due to the necessary preparations, this was only possible after two months.

The condition gradually deteriorated during the patient's stay in hospital. He again suffered from fever of unknown cause for some time. Blood cultures were negative the antistreptolysin-titre was not increased (100 U./ml.). Temperature did not fall after penicillin administration, but became normal on administration of 1.5 g. pyramidon daily. Subsequently, symptoms of right decompensation developed (namely, severe oedema, increased venous pressure). One day after changing beds, he suddenly became dyspnoeic and finally comatose, but recovered the next day.

He was treated with digitalis and diamox, to which he responded favourably. The oedema disappeared and he was no longer dyspnoeic. Then it was decided that the risk of an operation was justified, even if the prognosis was not favourable in view of the period of decompensation.

Discussion

The case-history of our patient corresponds with the observations in several similar cases. Dyspnoea of effort is the prominent feature, gradually increasing and due to pulmonary congestion. Later signs of right decompensation arise. Since in some cases murmurs are heard at the apex (also pre-systolic murmur), it is understandable that the diagnosis of mitral stenosis has often been made.[6, 10, 13, 17] Yet both the history and the course of the disease show peculiarities that as a rule are not encountered in a case of mitral stenosis.

In the first place the symptoms caused by changes in body position. As was demonstrated in our patient, acute dyspnoea and pre-cordial pain may suddenly occur after movement; even shock or comatose condition may

develop. Changes in position may give rise to sudden dizziness. Our patient, who had always slept on his right side, was no longer able to do so; sleeping was possible on his left side or back, but with the head elevated. The explanation of these symptoms is related with the mobility of the pedicled tumour in the left atrium, which may cause sudden serious circulatory disturbances. There is also a relationship with the variations in the physical signs that have often been described, e.g., a systolic murmur may be present in the lying position and a diastolic murmur in the sitting position, as already pointed out by Pawlowski (cf. Gottel). In our patient no murmurs were audible in the various positions.

The rapid progression of the decompensation symptoms is striking. It reacts poorly to treatment with cardiotonics[11, 19] which is unusual in mitral stenosis cases. Kirkey and Leren established the diagnosis ante mortem on the strength of variation of murmurs in different positions of the patient, and the rapid progression of the decompensation.

A remarkable observation in our patient was the *strong* pulsatory movements of the oesophagus at the level of the left auricle, synchronously with the ventricular action (Fig. 3); in our opinion, this fact is of diagnostic significance. This symptom is also absent in mitral stenosis. The systolic-positive excursion of the peripheral pulmonary curve without signs of mitral insufficiency can be explained by the mechanically ineffective auricular diastole, which is also of diagnostic significance. Finally, for the differential diagnosis it may be of interest that patients have no rheumatic fever in their history, but this also holds true in many cases of mitral stenosis. Moreover, some with myxoma had previously suffered from rheumatic affections.[15]

In other cases of myxoma cordis the emboli in the systemic circulation (brain, lungs, kidneys, extremities and in the coronary arteries) are of great importance,[5, 11, 19] sometimes causing death. These emboli, combined with cardiac murmurs and occasionally also with fever, were in several cases reminiscent of bacterial endocarditis,[5] but the blood cultures were always negative. In many cases the systolic blood pressure was low (less than 110 mm., even as low as 65 mm.),[17] but this sign was often lacking. Cardiac catheterization in our patient revealed high pressure values in the right ventricle and pulmonary artery; but this may be explained by pulmonary congestion and may also be found in mitral stenosis. The P.C.P. curve showed the picture known in mitral insufficiency and more especially if auricular fibrillation is present.

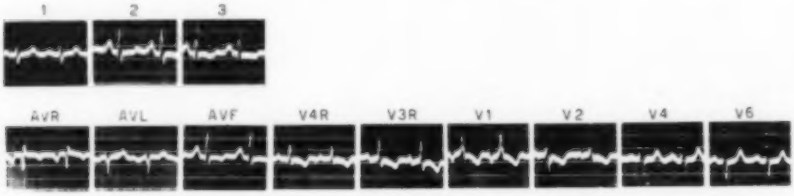

FIGURE 4: Electrocardiogram, right ventricular strain

Although history and changing physical signs provide important indications, it has been the angiocardiography which during the past few years has sometimes led to the correct diagnosis (left auricle),[11] (right auricle).[1, 3, 18]

In the contrast shadow of the auricle a gap is visible at the site of the tumour, if this is not too small. It is quite manifest in the second oblique

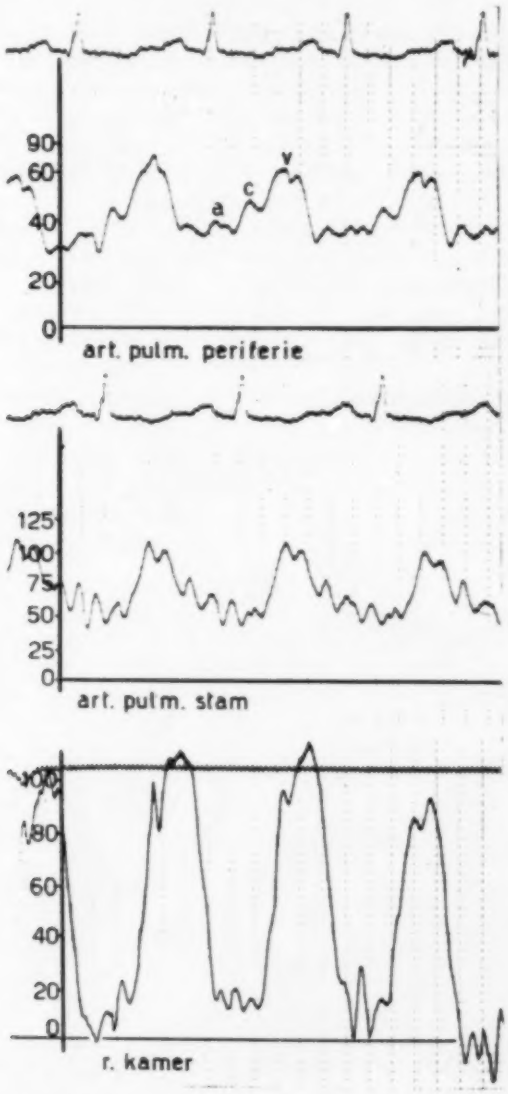

FIGURE 5: Pressure curves, pulmonary-artery periphery, pulmonary-artery trunk, and right ventricle.

position (left Fig. 6). In adults one should make exposures of 12-14 seconds, since the filling of the left auricle is retarded by the pulmonary congestion. This enabled us also to establish the diagnosis.

In the differential diagnosis malignant tumours of the heart should be mentioned, which are usually sarcomas and occur less frequently than benign ones. Sarcomas are generally situated in the right heart (auricle as well as ventricle). They show a more infiltrative growth, but may also be found as polypous tumours in the cavities of the heart. Obstruction of the superior vena cava and haemorrhagic pericarditis often occur in conjunction with these tumours observed by us twice. Metastatic heart tumours occur far more frequently (incidence 20-40 times as high[16]). They have already been diagnosed more often, also during life, based on occurrence of arrhythmias and haemorrhagic pericarditis in the presence of metastasizing tumour. Metastases may have originated from carcinomas of all major organs, especially of mammary glands, lungs, stomach, from skin melanomas and from lymphosarcomas. They may be situated in the right as well as in the left heart and often in both at the same time. They are rarely located in the valves.

Treatment

As operative removal of intracardiac tumours has so far been carried out in only a few cases, the results being still disappointing, it is desirable that new experiences be published. Only benign cardiac tumours can be considered for surgical removal. In the majority of cases these are the so-called myxomas or fibromyxomas, often pedicled, occurring in 25 per cent in the right atrium and in 75 per cent in the left atrium. They usually ori-

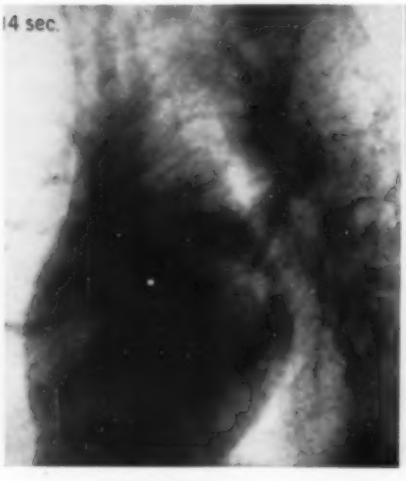

FIGURE 6A

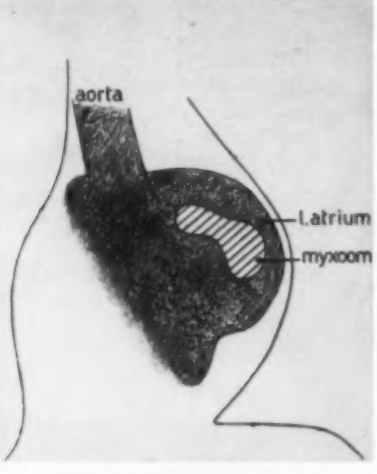

FIGURE 6B

Figure 6A: Angiocardiogram (14 sec.).—*Figure 6B:* None.

ginate from the septal wall. It further depends on the localization and size whether a benign tumour or cyst can be excised from the *cardiac wall*, as reported by Beck. Up to the time of writing, six cases of pre-operatively diagnosed myxoma cordis are known.[1, 2, 11, 18]

When operative treatment of the patient described was decided upon, we first considered which method of operation would be the best in this particular case. Study of the literature yielded the following facts:

Goldberg et al, reported two cases, one patient was operated on and died. Bahnson was no more successful with his patient. Ripstein operated on one patient under hypothermia, without result. Bailey operated on two, also with fatal issue, while Crafoord, in a personal communication to Goldberg, referred to a patient successfully operated in 1954, (July 16) with the aid of complete bypass with extracorporeal oxygenation and circulation.

On Bailey's advice we decided to operate under hypothermia, and were well aware of the fact that the chances of success were only slight, in view of the patient's age (45 years), serious pulmonary hypertension and the attack of decompensation.

Cardiac fibrillation was the imminent danger. The anaesthetists, therefore, were to try and keep the pH on the alkaline side during the ether-oxygen anaesthesia, by means of hyperventilation, because this consider-

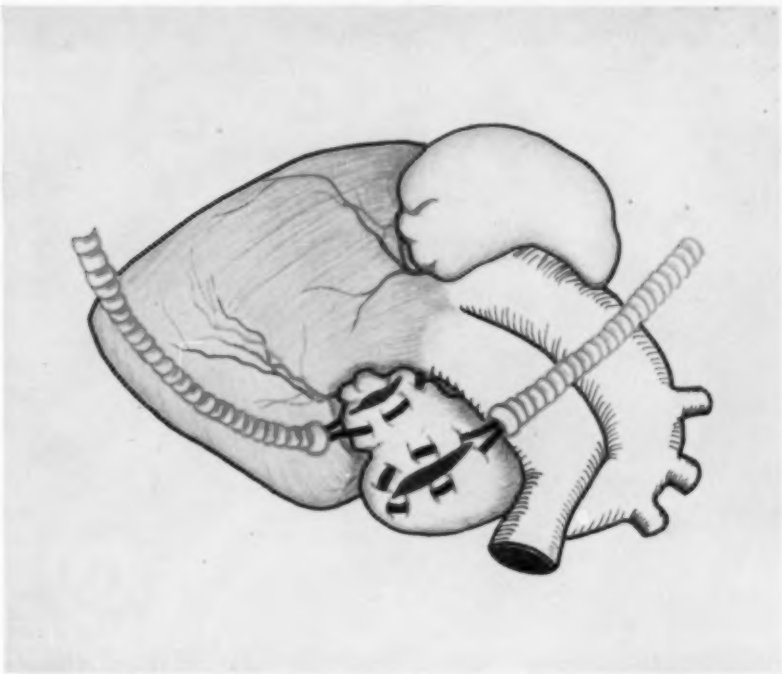

FIGURE 7: Tourniquets applied to the auricle and atrium and incisions used.

ably reduces the chances of ventricular fibrillation during operations under hypothermia.

We chose the immersion cooling technique as developed by Swan in Denver. During the operation, we were to be kept informed about the changes occurring during cooling by means of the ECG and regular determinations of the pH and alkali reserve (Brinkman et al.) and potassium determinations (Groen et al.). The patient was connected with an electrocardiograph, and transferred to the bath filled with water of 37° C. under intratracheal ether-oxygen anaesthesia after premedication with 15 mg. morphine, 0.25 mg., atropine and 100 mg. pracatal. When this was tolerated well, ice cubes were added for further cooling, and recording of the temperature and continuous ECG registration were started. The first blood sample (8:45 a.m.), taken while the patient was already in the bath and the temperature had fallen only 1°, yielded the following data: pH — 7.61 (18°) — 7.41 (37°). Alkali reserve — 31.4 vol. per cent. Plasma potassium 3.45 m.Eq./1. Arterial oxygen saturation 100 per cent.

Suddenly, when the patient's temperature had fallen not more than 1°, the ECG failed completely and the patient developed a pale colour, so that, evidently, acute cardiac arrest had set in. Blocking of the mitral ostium by

FIGURE 8: Myxoma extirpated from the left atrium (6.5 x 4 x 5 cm.).

the tumour had probably been an important cause in this event.

Taking a retrospective view, the severe acidosis (31.4 vol. per cent) should, of course, have made us hesitate to continue the operation, but we did not know this until the patient was already in the bath, and the pH was still normal due to the marked hyperventilation.

In operations under hypothermia it is tried to keep the pH on the alkaline side. From the beginning of the operation, the lungs are always markedly hyperventilated, which, in our patient, became manifest in the low carbon dioxide values recorded by the carbovisor (Brinkman) and the high oxygen saturation of the blood. We failed to realize sufficiently, however, that before the operation, in the medical clinic, mercurial diuretics and diamox had been used in the treatment of oedemata resulting from the cardiac decompensation, and that the acidosis was promoted by inhibiting the catalytic action of carbon-dioxide anhydrase (renal acidosis accompanied by hypopotassaemia). We had perhaps done better not to place the patient flat on his back in the bath, because, this probably promoted blocking of the mitral ostium. The patient was taken out of the bath after the occurrence of the asystoly, and placed on the operating table in the right lateral position. Unfortunately, some precious minutes were lost during this procedure. The thorax (there was left hydrothorax) was opened, also the pericardium (there was hydropericardium), and cardiac massage started at once. We succeeded in restoring the rhythm after some minutes. The blood pressure rose to 85 mm. Hg., his colour became good and it seemed that the acute danger had passed for the time being. A blood sample, obtained by puncture from the *left atrium*, yielded the following

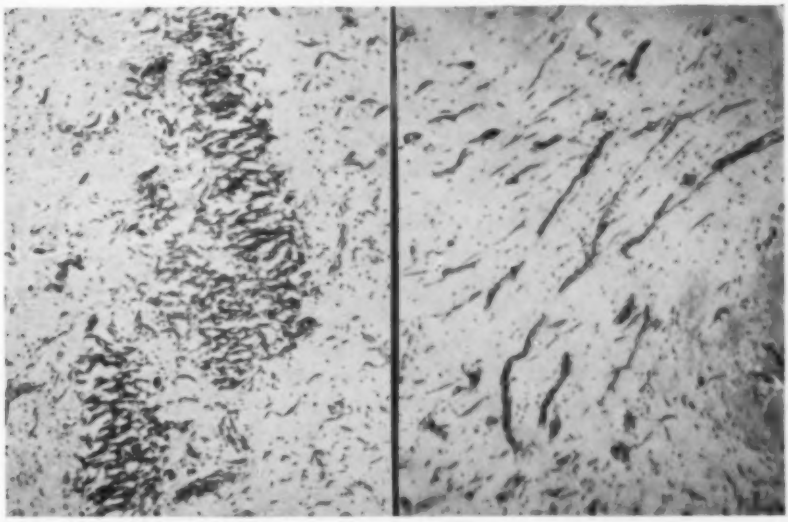

FIGURE 9A FIGURE 9B

Figure 9A: Photomicrograph of the myxoma.—*Figure 9B:* None.

particulars: pH. — 7.39 (18°) — 7.19 (37°), alkali reserve: 26 vol. per cent (normal 54-55 vol. per cent), plasma potassium 2.78 m.Eq./l), arterial oxygen saturation: 96 per cent.

This means that now there existed *marked acidosis*, no longer to be compensated by hyperventilation. There was also serious hypopotassaemia. We were advised to inject intravenously 400 ml. 6 per cent $NaHCO_3$ and 10 ml. 1 per cent KCl. Due to difficulties with the intravenous drip, this dose was not taken up completely.

After some deliberation it was decided to continue the operation, because stopping would involve too great risks due to the imminent blocking of the mitral ostium by the tumour.

A tobacco bag suture was laid around the base of the left auricle, and taken in a Rümmel tourniquet. Another tobacco bag suture in a Rümmel tourniquet was applied to a sound part of the left atrium where the incision was to be made (Fig. 7.). The auricle was opened and the atrium was palpated with the bare right index finger. A polypous short-pedicled tumour was found, lying with its lower pole on the mitral ostium. The pedicle was easily detached from the septum, the tumour was kept floating and pressed against the site where the left atrium was to be incised. The latter procedure was performed with the left hand, and the tumour was pushed through the opening without loss of blood, following which the tourniquet was tightened.

The course of the operation was excellent. The atrial wound was closed rapidly, as was the left auricle. We refrained from placing a clamp on the base of the aorta and pulmonary artery, because the operation proper seemed to become a successful and rapid procedure. Initially the heartbeat was good; it was slow and regular, but suddenly ventricular fibrillation arose. Electric defibrillation (0.1 sec., 240 volt, 1.5 amp.) brought the heart to a standstill, following which cardiac massage was again applied. We succeeded in getting the heart beating again, in which it struck us that the myocardium was rather lax. In the meantime the patient had been injected noradrenaline via the infusion (3 mg.). This procedure was repeated when ventricular fibrillation occurred anew. Success was again obtained, but it was of shorter duration. The blood pressure was finally no longer to be measured, and death followed after 10 ml. $CaCl_2$ had been injected intraventricularly in vain.

Looking backwards, we should not have started the hypothermia before the pH. and alkali reserve had been determined once more on the morning of the operation. If we had known of the acidosis and hypopotassaemia, we could have tried to combat the acidosis by administration of $NaHCO_3$, in which, of course, it is questionable whether thus the fatal issue could have been prevented with certainty. Probably the risk would have remained great indeed.

Taking everything into account, we were well aware that the patient would be exposed to great risks during an operation, but his future was also hopeless with conservative treatment. In the future, if the diagnosis

can be established early, and if the tumour exerts a less serious influence on heart and circulation, the issue will probably be more satisfactory in such cases.

Based on the pathological-anatomical findings, and in view of the fact that these "polypous" tumours are so often pedicled, operative treatment was already suggested earlier. If the operative removal is to be successful, however, it will be necessary, that the patient be operated on before decompensation had advanced too far. The operative technique in itself was satisfactory.

At necropsy of our patient (VOS) marked hypertrophy of the right heart with pulmonary congestion was found. There was no sign of air embolism. The site of the myxoma was only indicated, and was located near the foramen ovale. Marked hydrothorax and hydropericardium had already been observed during the operation. The description of the operative specimen (VOS) is as follows:

Macroscopically (Fig. 2). The tumour, extirpated from the left atrium of patient J. K. R., where it had been attached to the septum atriorum with a broad pedicle, measured 6.5 × 4 × 5 cm. The surface was smooth, shining, partly yellowish-grey and partly light reddish-brown. The tumour was soft and elastic, and proved to consist of fine, light yellowish-grey stripes on the cut surface.

Microscopically (Fig. 9). The greater part of the tumour tissue was composed of markedly oedematously swollen connective tissue, poor in cells and fibres, containing at some places narrow and scattered, and at other sites wide and closely packed parallel running connective tissue bundles with many capillaries. Some of these cell-rich parts were surrounded by areas poor in cells, somewhat reminiscent of mucinous tissue, but which did not give a mucin reaction, however, as is usual in such tumours.

In the present case no reason was found to doubt the blastomatous character, and to take this affection—as done by some investigators—for an organized thrombus.

Anatomical diagnosis: Myxoma cordis septi interatriati cordis in atrio sinistro.

SUMMARY

A case of pedicled myxoma cordis, originating from the septum of the left atrium in a 45-year-old man, in whom the diagnosis had been established pre-operatively is recorded. Operation was decided on because the patient had already suffered a severe attack of cardiac decompensation. The tumour, measured 6.5 × 4 × 5 cm., was removed under hypothermia. After the temperature had fallen 1° (immersion cooling) cardiac arrest arose, most probably due to obstruction of the mitral ostium by the lower pole of the tumour. Cardiac rhythm was restored by means of heart massage, and the operation was terminated *transatrially* without any loss of blood or air embolism. Unfortunately, ventricular fibrillation arose shortly afterwards; although this was overcome in the beginning, death was unavoidable due to repeated ventricular fibrillation.

RESUMEN

Se relata un caso de mixoma cardiaco pediculado originado en el septum atrial izquierdo en un hombre de 45 años en quien el diagnóstico se hizo antes de la operación. La operación se llevó a cabo porque el enfermo había sufrido ya un ataque severo de descompensación cardiaca. El tumor media 6.5 x 4 x 5 cms. y fué extraído bajo hipotermia. Después de que la temperatura había bajado 1° (enfriamiento por inmersión) hubo paro cardiaco, lo más probable debido a obstrucción del ortium mitral por el polo inferior del tumor. Se recuperó el ritmo cardiaco por el masaje y la operación se terminó por vía transatrial sin pérdida alguna de sangre y sin embolia gaseosa.

Desgraciadamente se presentó la fibrilación ventricular poco después y aunque ésta fué dominada al principio, la muerte se presento inevitablemente debida a la fibrilación ventricular reiterada.

RESUME

Les auteurs rapportent un cas de myxome cardiaque pédiculé provenant du septum de l'oreillette gauche, chez un homme âgé de 45 ans, chez lequel le diagnostic a été établi avant l'intervention. Celle-ci fut décidée parce que le malade avait déjà subi une attaque sérieuse de décompensation cardiaque. La tumeur, mesurant 6,5 x 4 x 5 cm. fut enlevée sous hypothermie. Après que la température fût tombée de 1° (refroidissement par immersion) un arrêt cardiaque survint, imputable le plus vraisemblablement à l'obstruction de l'orifice mitral par le pôle inférieur de la tumeur. Le rythme cardiaque fut rétabli grâce au massage du coeur et l'opération se termina à travers l'oreillette sans aucune perte de sang ou embolie gazeuse. Malheureusement, une fibrillation ventriculaire survint peu de temps après, et bien qu'elle ait été surmontée au début, sa répétition entraina la mort.

ZUSAMMENFASSUNG

Wiedergabe eines Falles eines gestielten Myxoms des Herzens, ausgehend vom Septum des linken Vorhofes bei einem 45 Jahre alten Mann, bei dem die Diagnose vor der Operation gestellt worden war. Zu der Operation hatte man sich entschieden, weil der Patient bereits einen schweren Anfall cardialer Dekompensation erlitten hatte. Der Tumor in den Ausmassen von 6,5 x 4 x 5 cm. wurde unter Hypothermie entfernt. Nachdem die Temperatur 1 Grad gefallen war, (Kühlung mit Immersion), kam es zu einem Herzstillstand, höchstwahrscheinlich infolge Verstopfung der Mitralöffnung durch den unteren Pol des Tumors. Die Herztätigkeit kam wieder zustande mittels Herzmassage, und die Operation wurde zu Ende geführt vom Vorhof aus ohne irgend welchen Blutverlust oder Luftembolie.

Unglücklicherweise trat kurz danach Kammerffimmern auf; obwohl dies sich zu Anfang überwinden, liess, war der Tod unvermeidlich infolge wiederholten Kammerflimmern.

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Evaluation of Results After the Administration of Drugs in the Presence of Resistant Mycobacterium Tuberculosis*

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Introduction

Current literature is rich in reports on resistance developed by tubercle bacilli to antituberculous drugs *in vitro* and its possible significance. Efforts are being made in order to correlate resistance *in vitro* with clinical findings.

Some authors believe that drugs should be discontinued once an absolute resistance is demonstrable (100 mcg./ml.) since thereafter there will be no improvement imputable to them; others taking the opposite view, feel that even in the presence of apparent resistance, it is possible for the patient to harbor strains susceptible of being affected by the continued action of therapeutic agents. This study analyzes the results of the continuation of the drugs in the confirmed presence of resistant bacilli in order to determine:

1. *Time* of appearance of resistance.
2. *Clinical* and radiological changes.
3. *Bacteriological conversion.*

A limited experience with Viomycin is also reported.

Material and Methods

Two hundred and seventy seven patients with active pulmonary tuberculosis with positive sputa and/or gastric washings for Mycobacterium tuberculosis admitted to the Chest Service, Gorgas Hospital, from June 1, 1949 through December 1954 have been evaluated.

No attempt was made to classify the disease according to extent or type of lesions, since our only object was to observe changes under the conditions described previously.

Every six weeks, the patients were submitted to periodic examinations or evaluations consisting of: clinical observations (fever, cough, weight, toxicity, etc.); x-ray films of the chest (posterio-anterior); three sputa examinations on direct smears and concentration for M. tuberculosis followed, if negative, by three gastric or bronchial washings.

Each specimen was submitted to the following tests:

1. *Direct Smear*: Using Ziehl-Nielsen stain.

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2. *Concentration*: Using standard digestive mixture.
3. *Culture*: The culture on Petragnani media was observed for a total of 90 days before discarded as negative.
4. *Sensitivity test*: Two dilutions (10 mcg. and 100 mcg.) of the drug used were done. Seven tubes were inoculated with the growth from the original culture. Two tubes for each drug to be studied and one plain tube with culture media that served as a control. Positive growth in any tube that was confirmed morphologically, by the Ziehl-Nielsen stain gave us the sensitivity for that particular drug. Growth of acid-fast bacilli in a dilution of 100 microgram/ml. was considered absolute resistance to the drug.

Results

A total of 277 patients were evaluated according to the following criteria:

1. Those who received one or more drugs
2. Those who developed resistance to one or more of the drugs used.
3. Observation of patients on whom drugs were continued in the presence of resistant bacilli, as to:
   A. Clinical and radiological changes.
   B. Permanent bacteriological conversion.
   C. Toxicity due to the drugs.
   D. Other forms of treatment and changes attributable to them.
   E. Reactivations and deaths.

Three cases received only streptomycin. After 30 to 90 days, with an average of 40 days, they all developed resistant bacilli. On continued administration of the drug, no clinical or radiological improvement was observed and sputa continued positive in all three patients. They received at the same time pneumoperitoneum with no demonstrable benefit.

TABLE I
TOTAL CASES: 162
Resistances: 20 (49.3 Per Cent)

Streptomycin	PAS	SM—PAS
11 Cases—6.7 Per Cent	3 Cases—1.8 Per Cent	66 Cases—40.8 Per Cent

All resistances were permanent.

One hundred and sixty-two patients received the combined and intermittent treatment of streptomycin and para-aminosalicylic acid. Of these, 80 (49.3 per cent) developed resistant bacillus to one or both drugs. Eleven (6.7 per cent) were resistant to streptomycin; three (1.8 per cent) to PAS and 66 (40.8 per cent) to both drugs.

TABLE II
APPEARANCE OF RESISTANCE

Streptomycin		PAS		SM—PAS	
Days	Average	Days	Average	Days	Average
0-240	130	30-360	260	0-408	133

0 = Natural or spontaneous resistance.

The average time for the development of resistance to streptomycin was 130 days; to PAS was 260 days and for both drugs simultaneously was 133 days.

TABLE III
DRUGS CONTINUED IN 42 CASES

	Clinical Improvement		Radiological Improvement		Permanent Bacteriological Reversion	
	Yes	No	Yes	No	Yes	No
No. of Cases	29	13	14	28	22	20
Per Cent	69	31	33.2	66.6	52.3	47.6

These drugs were given to 42 of the 80 resistant cases, noticing that 29 (69 per cent) showed clinical improvement; 14 (33.2 per cent) radiological improvement and 22 (52.3 per cent) a permanent bacteriological conversion.

TABLE IV

Other Therapy	Cases	Improvement
Isoniazid	2	2
Pneumoperitoneum	30	5
Pneumothorax	5	0
Thoracoplasties	3	2
Segmental Resection	1	1
Lobectomy	5	5
Pneumonectomy	1	1

Reactivation: 4 Deaths: 4

Thirty of the 42 cases received pneumoperitoneum; five pneumothorax; three thoracoplasties; one was submitted to segmental resection and in two cases isoniazid was added. The clinical and radiological improvement and bacteriological conversion can be attributed in some cases to the following: two cases to isoniazid; five, to lobectomies; and in one, to pneumonectomy. In this group there were four reactivations and four deaths due to tuberculosis.

TABLE V
TOTAL CASES: 17

Resistance to INH	15	(88.2 Per Cent)
Appearance of Permanent Resistance	Average:	0-180 Days 123 Days

0 = Natural or spontaneous resistance.

Seventeen patients received only isoniazid. Of these, four were initial cases while 13 had already shown resistant bacilli to streptomycin and to PAS. Isoniazid was started on these patients as a last resort because they had chronic, advanced, and predominantly productive lesions. Fifteen (88.2 per cent) developed resistant bacilli to INH in an average of 123 days. Two of these showed resistant bacilli before starting the drug, presenting so called natural or spontaneous resistance.

TABLE VI
INH CONTINUED IN 15 CASES

	Clinical Improvement		Radiological Improvement		Permanent Bacteriological Revision	
	Yes	No	Yes	No	Yes	No
No. of Cases	13	2	1	14	3	12
Per Cent	86	14	6	94	20	80

Of the 15 resistant cases, 13 (86 per cent) showed marked clinical improvement; one (6 per cent) radiological improvement; while three (20 per cent) had permanent bacteriological conversion.

TABLE VII

Other Therapy	Cases	Improvement
Pneumoperitoneum	7	2
Lobectomy	1	1

Reactivation: 0 Deaths: 0

Seven received pneumoperitoneum as additional treatment and only two cases improved. One had lobectomy showing clinical, radiological and bacteriological improvement after surgery.

TABLE VIII
TOTAL CASES: 49
Resistances: 9 (18.3 per Cent)

	SM	INH	SM—INH
No. of Cases	4	2	3
Per Cent	8.1	4	6.1

All permanent resistances.

Forty-nine patients received combined treatment of isoniazid and streptomycin. Nine (18.3 per cent) developed resistant bacilli to either drug. Four (8.1 per cent) were resistant to streptomycin; two (4 per cent) to isoniazid and three (6.1 per cent) to both drugs simultaneously.

TABLE IX
APPEARANCE OF RESISTANCE

SM		INH		SM—INH	
Days	Average	Days	Average	Days	Average
90-120	105	90-160	125	90-160	83

One hundred and five days was the average time for the appearance of resistant bacilli to streptomycin; 125 days for isoniazid and 83 days for both drugs at the same time.

TABLE X
DRUGS CONTINUED IN NINE CASES

	Clinical Improvement		Radiological Improvement		Permanent Bacteriological Revision	
	Yes	No	Yes	No	Yes	No
No. of Cases	6	3	6	3	6	3
Per Cent	66.6	33.3	66.6	33.3	66.6	33.3

Clinical and radiological improvement was noted in six patients (66.6 per cent) and a permanent bacteriological conversion in the same. The three cases that didn't show improvement are the same that were resistant to both drugs simultaneously.

TABLE XI

Other Therapy	Cases	Improvement
Pneumoperitoneum	3	3
Pneumonectomy	1	1

Reactivation: 0 Deaths: 1

Three patients received pneumoperitoneum and one had a pneumonectomy. The three who received pneumoperitoneum improved after starting this therapy and the other, after pneumonectomy. In this group there was no reactivation but there was a death caused by myocardial infarction.

TABLE XII
TOTAL NUMBER OF CASES: 46
Resistances: 14 (30.7 Per Cent)

	INH	SM	PAS	SM—PAS	INH—SM—PAS
No. of Cases	0	1	0	3	10
Per Cent	0	2.2	0	6.5	22

All permanent resistances

Forty-six patients received the combined therapy of isoniazid, streptomycin and PAS —Of these, 14 (30.7 per cent) showed resistant bacilli to one or more drugs.

TABLE XIII
APPEARANCE OF RESISTANCE

INH		SM		PAS	
Days	Average	Days	Average	Days	Average
30-240	103	30-240	105	30-240	110

The time for development of resistance to each drug was approximately the same.

TABLE XIV
DRUGS CONTINUED IN 14 CASES

	Clinical Improvement		Radiological Improvement		Permanent Bacteriologic Revision	
	Yes	No	Yes	No	Yes	No
No. of Cases	11	3	7	7	6	8
Per Cent	78	22	50	50	43	57

After continuing the administration of these drugs, only 11 (78 per cent) showed clinical improvement. Seven (50 per cent) had slight or marked radiological improvement and six (43 per cent) permanent bacteriological conversion.

TABLE XV

Other Therapy	Cases	Improvement
Pneumoperitoneum	3	0
Lobectomy	4	2
Pneumonectomy	2	1

Reactivation: 0 Deaths: 4

Besides the mentioned drugs, three patients received pneumoperitoneum without improvement; two with lobectomies and one with pneumonectomy improved. There was no reactivation in this group, but four deaths; two, due to tuberculosis; one, to an anaphylactic shock due to cocaine during bronchoscopy and the other of tension pneumothorax after lobectomy.

*Viomycin**

Viomycin is an antituberculous agent derived from a strain of streptomycin puniceus, discovered by Finlay and collaborators. According to some authors it is effective against streptomycin-sensitive as well as resistant tubercle bacilli.

The original studies completed in animals and human beings indicated that in adequate therapeutic concentrations the drug is toxic. Nevertheless, more recent invstigations have revealed that used in lower dosages and employing an intermittent regimen, toxicity does not represent a problem. It has an antituberculous effectivity greater than PAS but less than streptomycin or isoniazid.

On the strength of favorable reports, such as those of Tucker, Amberson, et al, and those of the Tenth and Eleventh Veteran Transaction on the Chemotherapy of Tuberculosis, 10 patients were started on treatment with this drug, in May of 1953. These patients were suffering from pulmonary tuberculosis, far advanced, of mixed type and with resistant bacilli to isoniazid, streptomycin, and para-aminocalicilic acid. They were as it can be readily seen "cases in extremis." Two daily doses of 2 grams each of viomycin sulphate intramuscularly, three times a week were administered. After four months on this regimen, no clinical, nor radiological improvement was observed and all the cases continued with positive sputum.

*The Viomycin used in this investigation was donated by Pfizer Corporation.

No apparent toxicity caused by the drug was observed, however all patients complained of marked pain at the site of injection, making it necessary to add novocaine to the solution prior to injection. This observation does not constitute an adequate evaluation of the drug, because the cases, besides being few in number, were all "abused" with the other chemo-antibiotic agents. Even so, results seem to confirm partially the fact that viomycin should not be employed alone, and it should not replace the other antituberculous drugs in use today.

Discussion

It is again confirmed that the appearance of resistances occurs much earlier when the chemo-antibiotic agents are administered alone, than when given combined with one or more other drugs. It is therefore deduced that from a purely medical standpoint, the administration of a single drug in the treatment of tuberculosis is not to be recommended.

Once absolute resistance is demonstrable, there is no clinical, radiological improvement, nor bacteriological conversion attributable to the continuation of drugs. The improvement obtained from the time of appearance of resistances must be considered as due to other factors, such as complete bed rest, temporary interventions, such as artificial compression therapy or permanent ones, as surgery. In some cases of resistance to one drug the improvement is observed upon changing to another chemo-antibiotic agent. It is to be accepted that in cases that have received more than one drug the improvement is due to all drugs until resistance is demonstrated, and from then on to those agents to which the bacilli are still susceptible.

Notwithstanding the above statements, it is admitted that when the drugs were continued in the presence of resistances, and surgical interventions were performed, extensions and disseminations were practically unknown, particularly if compared with the frequency of this type of complication in the pre-antibiotic era. In the administration of isoniazid, it is observed that the clinical improvement continues, and becomes permanent in spite of the presence of resistant bacilli and even if there is no evidence of radiological improvement or bacteriological conversion. With the patient in a better general condition and having increased considerably his organic resistance, it is possible to perform surgical procedures with success and less possibilities of complications.

Other patients, not subjected to surgical interventions become stabilized and chronified and although there is no further progress in their improvement they do not seem to get worse becoming what has been termed "good chronics," which continue to constitute a serious therapeutic challenge and public health problem that remains without solution.

The dosages and drug administration routines followed were the ones accepted internationally. Maybe with the idea of obtaining greater clinical radiological or bacteriological benefits the dose could have been increased, but it has been proved that by so doing, only greater toxicity without more efficiency is obtained, as we were able to demonstrate in a previous paper.

In this study, only four (1.4 per cent) of the patients presented evidence of toxicity. Two reacted to streptomycin, one of them showing irreversible injury to the eighth nerve, and the other, together with the patients that reacted to isoniazid and PAS, the symptoms disappeared entirely on discontinuation of the drugs.

It is convenient to point out that in some samples of sputa which were positive on direct smear and concentration, no positive culture was obtained. Maybe if other culture media would have been employed together with the Petragnani, which was used in this observation, a higher percentage of positive cultures would have been obtained. This phenomenon could also be explained by the fact that some strains of Mycobacterium tuberculosis lose their vitality and virulence with the appearance of resistance and their growth becomes more difficult. Today, there is under discussion in the literature, the theory that with an increase in resistance there is decrease in the degree of virulence of these organisms to such an extent that some resistant strains lose their capacity to produce progressive disease in highly susceptible animals. We injected 10 guinea pigs with material in which resistant bacilli to all drugs used were demonstrated. When these animals were sacrificed at the end of six weeks, generalized tuberculosis was found in eight while in two, there was *no* demonstrable disease. These results do not seem to confirm the aforementioned theory.

CONCLUSIONS

1. Two hundred and seventy patients with pulmonary tuberculosis admitted to the Chest Service of Gorgas Hospital from June 1949 through December 1954 were evaluated.

2. Clinical, radiological and bacteriological results were analyzed on those patients that developed resistant bacilli to the antituberculous drugs.

3. The fact that the development of resistance occurs earlier when these agents are administered alone than when given combined with one or more is again confirmed; therefore, from a purely medical standpoint, the use of one drug alone, including viomycin is not to be recommended.

4. Once resistance appears, there is no clinical, radiological, or bacteriological improvement that can be attributed as due to the chemo-antibiotics agents.

5. Even in the presence of resistant organisms, the chemo-therapeutic agents prevent extensions and disseminations as the result of surgical interventions and they stabilize the lesions on the so called "good chronics."

6. Toxicity to the drugs was found in four (1.4 per cent) of the cases. Only one had permanent damage.

CONCLUSIONES

1. Se estudiaron doscientos setenta enfermos de tuberculosis pulmonar que se admitieron en el Servicio de Tórax del Hospital Gorgas de Junio de 1949 a Diciembre de 1954.

2. Se analizaron los resultados de estudios clínicos, radiológicos y bacteriológicos de aquellos enfermos que presentaron bacilos resistentes a las drogas antituberculosas.

3. Se confirmó nuevamente el hecho de que la resistencia a las drogas ocurre más temprano cuando se administra una droga sola que cuando se administran combinadas una o más. Por tanto, desde el punto de vista meramente médico, el uso de una sola droga, incluyendo de la Viomicina, no se recomienda.

4. Una vez que aparece la resistencia, deja de haber mejoría clínica, radiológica o bacteriológica atribuible a los agentes quimioterápicos.

5. Aún en presencia de organismos resistentes, los medicamentos quimioterápicos evitan las extensiones y diseminaciones como resultados de las intervenciones quirúrgicas y estabilizan las lesiones de los llamados "buenos crónicos."

6. Se encontró toxicidad de las drogas en cuatro casos (1.4 por ciento). Sólo en uno hubo daño permanente.

RESUME

1. L'étude porte sur 270 malades atteints de tuberculose pulmonaire, admis au service des affections thoraciques du Gorgas Hospital entre juin 1949 et décembre 1954.

2. Les auteurs ont noté les résultats cliniues, radiologiques et bactériologiques obtenus chez les malades dont les bacilles étaient résistants aux médications antituberculeuses.

3. Ils confirment de nouveau le fait que le développement de la résistance survient plus précocément lorsque les agents chimio-thérapiques sont administrès isolément que lorsqu'ils sont donnés en association de deux ou de plusieurs produits. C'est pourquoi, du strict point de vue médical, l'utilisation d'un produit isolé, y compris la viomycine, ne doit pas être recommandé.

4. Une fois que la résistance est apparue, il n'y a aucune amélioration clinique, radiologique ou bactériologique qui puisse être attribuée aux agents chimio-antibiotiques.

5. Même quand les microbes sont résistants, les agents chimio-thérapiques empêchent l'extension et la dissémination après les interventions chirurgicales, et ils stabilisent les lésions des malades que l'on considère comme de "bons chroniques."

6. La toxicité des produits ne se révéla que chez quatre malades (1,4%). Dans un seul cas, elle causa des troubles définitifs.

SCHLUSSFOLGERUNGEN

1. Auswertung von 270 Kranken mit Lungentuberkulose, die in die Thorax-Abteilung des Gorgas Hospitals von Juni 1949 bis Dezember 1954 eingewiesen worden waren.

2. Klinische, röntgenologische und bakteriologische Befunde wurden bei denjenigen Kranken näher untersucht, bei denen sich gegen antituberkulöse Heilmittel resistete Bazillen entwickelt hatten.

3. Die Tatsache wird wiederum bestätigt, dass die Entwicklung einer Resistenz früher einsetzt, falls diese Medikamente allein gegeben werden, als wenn sie mit einem oder mehreren anderen Mitteln kombiniert werden;

es kann daher vom rein ärztlichen Standpunkt die Verwendung einer Substanz allein einschliesslich Viomycin nicht empfohlen werden.

4. Tritt erst einmal Resistenz ein, dann kommt es zu keiner klinischen, röntgenologischen oder bakteriologischen Besserung, die den chemotherapeutischen oder antibiotischen Substanzen zugeschrieben werden kann.

5. Selbst bei Vorliegen resistenter Keime verhindern die chemotherapeutischen Stoffe Ausbreitung und Streuung im Gefolge chirurgischer Eingriffe, und sie stabilisieren die Herde zu den sogenannten chronischen Asylierungs fälle.

6. Medikamentöse Schädigungen wurden in 4 = 1,4% der Fälle gefunden. Nur einmal kam es zu einer Dauerschädigung.

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The Clinical Problem of Adiposity of the Heart and Cardiac Enlargement of Undetermined Etiology

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The purpose of this report is twofold—first, to present a probable case of adiposity of the heart diagnosed clinically; and secondly, to again direct attention in the differential diagnosis of unexplained cardiomegaly to this entity which, to the author's knowledge, has heretofore been only a post-mortem diagnosis.

Such a presentation appears to be timely in view of the practically complete absence of a discussion on this subject in the literature and standard cardiology texts of the past one to two decades. This is all the more impressive at a time when the problem of obesity and its complications is of such vital concern to all practicing physicians. Almost every paper written by those internists and cardiologists who have recently reviewed the effects of obesity on the cardiovascular system makes no mention of this condition. In fact, in a comprehensive article entitled, "Unusual Forms of Heart Disease," which appeared in a cardiology journal as late as October, 1954, the only reference to this entity was in the form of two words, "possibly obesity," under the classification of "conditions precipitating or accelerating the development of the more usual forms of acquired heart disease."[1] As another manifestation of the obscurity of this condition nowadays, Dr. Paul White recently stated that although he had made mention of it in his textbook, he had never personally recognized such a case.[2]

One cannot help but agree with Burchell that many of those rarer cardiac conditions, which do indeed lend spice to the diagnostics of cardiology, could be all but forgotten, and possibly without loss, in the daily practice of medicine. His statement that unusual manifestations of common diseases probably mislead the physician more often than do unusual diseases, however, also holds much truth and import, particularly if a specific treatment is available as in the case of obesity.[1]

Like so many other unusual diagnoses, this condition, variously labeled as adiposity of the heart, cor adiposum, the fatty heart, lipomatosis of the heart, lipomatosis cordis and fatty infiltration of the myocardium, has had its cyclic periods of interest and popularity, *but primarily as reports dealing with post-mortem findings.* Among the last significant papers written on the subject, two appeared in the same volume of the *Archives of Internal Medicine* published in 1933.[3, 4]

The pathological findings in the fatty heart have been classically set forth by Corrigan and Saphir. In an analysis of the 58 necropsied cases reviewed with evidence of fatty infiltration of the myocardium, the usual site of the predominant infiltration was in the right ventricle.[3] Others have confirmed this observation. The interventricular septum may be involved to the degree of producing an actual complete heart block.[5] Frequently,

entire sections of the myocardium may be completely replaced by the fat, most likely originating from the pre-existing subepicardial fat. There ensues a compression and atrophy of the adjacent myocardial fibers and an obliteration of the usual sharp line of demarcation between the subpericardial fat and myocardium.[6] Since the infiltration is less striking in the left ventricle and in the subendocardial areas, it has been postulated that the fat originated not from direct infiltration, but rather from the transformation of pre-existing fibrocytes *in situ* into fat cells.[5]

It is of interest that although normal heart muscle contains no visible fat, it yields 15 per cent of fat when extracted with ether.[7] It should be emphasized at this point that the present report does *not* refer to the "fatty degeneration" of the heart noted in severe infections or anemia, as classically exemplified by the gross speckled "thrush breast" appearance. Although the pathology of the heart in adiposis dolorosa has not been adequately reviewed, several authors have referred to the occurrence of fatty infiltration with cardiomegaly and congestive heart failure.[8, 9]

This condition was considered as the sole cause of death in two of the patients reported by Saphir and Corrigan and in the case of Spain and Cathcart, primarily due to either heart failure or heart block. Attention has been directed to the possible untoward effects of anesthesia. Adiposity of the heart may also be a contributing cause of death, since it may produce a severe type of acute congestive heart failure if a poor cardiac reserve is already present; or it may be entirely unrelated as, for example, in postmortem examinations on emaciated patients. It may be recalled that considerable discussion has focussed upon the enlarged hearts of heavy beer and malt drinkers, especially in Europe, in which the disorder has been diagnosed variously as cardiac hypertrophy, beri-beri and nutritional heart disease.[10] Since these patients are often obese, Karsner has elaborated upon the possibility that the alcohol, being readily oxidized itself and possibly depressing other oxidation processes, may protect fats and permit their accumulation.[6]

Case Report: V. S. B., a 30 year old married white industrial engineer, was referred for a diagnostic cardiac evaluation in 1954. He had been inducted into the Navy in 1947, when a routine chest x-ray film revealed the heart to be of normal size. A routine x-ray film on September 27, 1949, following his return from overseas duty, revealed an enlarged cardiac shadow. He was studied at the local dispensary and at a United States Naval Hospital where the only significant finding was the same enlarged cardiac shadow noted on x-ray film. He was returned to duty without subsequent difficulty. Prior to discharge from the service, he was again noted to have a heart size "20 per cent above that predicted for his height and weight." Although he did have a vague history of some stiffness of the fingers at an early age and occasional colds and mild sore throats, there was no actual stigma of rheumatic fever, hypertension, coronary disease, or congenital defects. During a special cardiac consultation on December 29, 1951, the possibility of both congenital and rheumatic etiologies were considered.

From the period of 1947 to 1949, while he continued to be active in Navy athletics, his weight increased from approximately 179 to 230 pounds. He had persisted at that weight. It should be noted that he had always been active in all the strenuous forms of competitive athletics. Since discharge from the service, however, he had assumed a more or less sedentary occupation on the advice of the Navy and consultant physicians, although there were actually no symptoms referable to his cardiac or pulmonary systems. His past and family history was essentially nonrevealing, except that his elderly father has vague "heart trouble" of an undetermined nature. Five siblings are living and well. He had also been experiencing fairly typical migraine headaches intermittently for about six years. No other paroxysmal complaint was present to suggest an underlying pheochromocytoma or insulinoma.

Physical Examination

The patient was an obese white male appearing his stated age and in no apparent acute or chronic distress. He was hyperkinetic, cooperative, and quite reliable. Height 5′11″; weight 230 pounds. Temperature 98° F., pulse 76 and regular. Blood pressure 120/66. The significant findings were as follows: The fundal vessels were within normal limits. The thyroid gland was not remarkable. The heart was minimally enlarged by percussion, and a prominent apical impulse was felt outside the mid-clavicular line in the fifth left anterior interspace. The sounds were of good quality with A2 being greater than P2; no murmur was noted. The chest was clear. There was a healed right appendectomy incision. No clubbing, cyanosis or arthropathy were noted. The pedal pulses were palpable bilaterally. The skin was not remarkable in its texture or sweating.

Laboratory Data

The urine concentrated on random specimens to 1.020. There was an occasional trace of albumin (probably related to some of the pyelography dye he had received); the sediment was not remarkable. Blood serology negative. The white blood cell count was 7500 with 43 per cent neutrophils, 49 per cent lymphocytes, 2 per cent eosinophils. The hemoglobin was 15.0 gms. per 100 ml. The hematocrit was 44 per cent. The blood urea nitrogen was 18 mg. per 100 ml. A blood sugar level two hours after eating was 110 mg. No LE cells were noted. Total blood cholesterol 156 mgs. per cent. Total protein 7.3 grams per cent with an A/G ratio of 4.1/2.2. Sedimentation rate 7 mm. per hour. Serum iron 89 mcg.; total iron binding capacity 237 mcg.; percentage saturation 37.

X-ray and Other Data

Numerous chest x-ray films revealed an apparent left ventricular enlargement with slight prominence of the pulmonary artery segment on the left cardiac border and with a somewhat smaller aortic knob. A barium swallow and fluoroscopy of the cardiac shadow revealed bilateral enlargement, particularly of the left ventricular outflow area, but no definite enlargement of the auricles. The esophagus was not displaced. Tomograms of the heart did not show any change in density of the cardiac shadow or calcification of the valves or myocardium. Skull x-ray films were within normal limits. Intravenous pyelograms were not remarkable. An upper gastrointestinal series was within normal limits.

Electrocardiograms revealed a right bundle branch block pattern with occasional interpolated unifocal ventricular extrasystoles. No changes in the T-waves or the ventricular complexes following the extrasystoles were noted. Otherwise the tracings were considered to be within normal limits. A simultaneous *ballistocardiogram* and electrocardiogram revealed a somewhat widened I-J interval in some complexes, but otherwise the tracing was within normal limits. This apparent abnormality was due to the mechanical activity of the true interpolated premature ventricular systoles. A two-step test produced no significant changes following the standard exercise.

Clinical Course

He remained afebrile and asymptomatic throughout his hospital stay. Repeated blood pressure determinations revealed the highest reading to be 120/90, and averaged 110/60. He had also been seen in consultation with several other cardiologists who concluded that he had heart disease with cardiac enlargement, the cause of which was not apparent. It was felt that he did not have either a pericardial cyst or other mediastinal mass, and that the abnormality did not represent an epicardial fat pad. The risks of angiocardiography and cardiac catheterization studies were considered not to be justified at present.

It was the author's opinion that the cardiomegaly was possibly related to "adiposity of the heart" in view of the history of such a profound weight gain just prior to the cardiomegaly having been noted, and in the absence of stigmata of rheumatic, coronary, hypertensive or congenital heart disease. Similarly, in the absence of angina or other cardiac symptoms and in the presence of normal T-waves, it was felt that such diagnoses as chronic myocarditis and fibroelastosis of the endocardium could not be entertained. It was not known whether the right bundle branch block pattern represented fatty infiltration of the interventricular septum or was merely the normal variant not infrequently found in otherwise healthy young men. Since his entire family lived in Utah, x-ray and electrocardiographic studies of them could not be pursued. He was placed on a vigorous weight reduction program.

The first follow-up occurred two months later. He had lost 20 pounds of weight and felt perfectly well. His pulse and blood pressure both at rest and after exercise were normal. A chest x-ray film revealed a decrease of 1.5 cm. in the transverse diameter of the heart. The right bundle branch block was the only abnormality noted on the electrocardiogram. At six months follow-up, he had lost a total of 45 pounds. He had remained active and asymptomatic. No further changes in either his x-ray films or electrocardiogram were noted.

Discussion

This patient again brings to attention the perplexing problem of "cardiac enlargement of undetermined etiology." Its prominent position in the diagnostics of cardiology has in no small measure been due to the significant number of such asymptomatic individuals who have been discovered as a result of routine chest x-ray films or mass x-ray film surveys. The report by Hyman of a group of 350 asymptomatic men within the age range of 17 to 51 years who were restudied because of some objective cardiac abnormality after voluntary enlistment for either the Navy or Marine Corps exemplifies this experience.[11] After careful investigation, 26 of these candidates could only be diagnosed as "simple enlargement of the heart." No correlation curves could be drawn from the size of the heart, electrocardiographic findings, blood pressure, or exercise tolerance curves.

It goes without saying that the vast majority of persons with cardiac enlargement will be found to have either coronary, hypertensive, rheumatic, congenital or syphilitic heart disease. That uncomplicated coronary artery

disease may—and commonly does—result in significant cardiac hypertrophy has been independently well documented by both Master[31] and Connelly and Littmann.[32] As an aid in the differential diagnosis of cardiomegaly due to the less common forms of heart disease, Burchell has presented the following classification:

(a) rare anatomic conditions, for example, Ebstein's malformation of the tricuspid valve, traumatic rupture of a valve, primary neoplasm;

(b) heart affected as an integral part of a general disease, for example, amyloidosis, lupus erythematosus, scleroderma, hemochromatosis;

(c) cardiac complications of other diseases, for example, diphtheria, purulent pericarditis, sickle cell and other anemias, thyrotoxicosis (both overt and occult) arteriovenous fistula, myocardial metastasis;

(d) conditions precipitating or accelerating the development of the more usual forms of acquired heart disease, for example, xanthomatosis, possibly obesity, myxedema; and

(e) conditions mimicking primary heart disease, for example, thrombosis or involvement of the inferior vena cava by tumor.

To this group may be added several other disease entities resulting in cardiomegaly, many of which have been more recently in vogue. These include endomyocardial fibroelastosis, idiopathic cardiac hypertrophy, chronic myocarditis, the "athletic heart," Friedreich's disease and familial cardiomegaly. Amongst the other pathophysiologic and biochemical entities are prolonged bradycardia (with or without heart block), prolonged tachycardia, pulmonary embolism with cor pulmonale, and Von Gierke's disease. For the purpose of both completeness and interest, reference is also made to the even rarer conditions of "congenital dilatation of the heart" in adults[12] and the so-called "parchment heart."[13] Before proceeding further, this listing should be qualified by the fact that every experienced clinician has encountered patients with symptoms due to an unexplained large heart in whom a definite diagnosis was impossible, either because the patient recovered or due to the paucity of specific findings even at a postmortem examination.[35]

Endomyocardial fibroelastosis of the infantile, childhood and adult types has received considerable attention recently.[14-16] As a result of the thickened endocardium, a situation is produced that is analogous physiologically in many respects to that of chronic myocardial fibrosis and chronic constrictive pericarditis. Mechanical inefficiency, impairment of conduction, and myocardial and vascular hypoxia occur, followed by a compensatory myocardial hypertrophy and dilatation.[17] In a series of 20 autopsied cases culled from 10,000 autopsies and 24 cases of "chronic heart disease with hypertrophy of uncertain etiology" at the Massachusetts General Hospital, Thomas and his colleagues noted that none showed the contracted type of fibroelastosis with the small left-sided chambers such as had been previously described in infants.[16] On the contrary, marked dilatation of most of the chambers was found. Our experience with such a case confirms the rapid and fatal progression of dyspnea, cyanosis and heart failure which has characterized most of the reported cases.[18] In this regard, however, White

and Fennell have recently described a patient who died of this condition at the age of 71 after experiencing angina pectoris for 15 years and congestive failure for two years. They also describe the similarly protracted case history of a 53 year old man with the same complaints.[19] It would appear that many cases which had previously been diagnosed as "idiopathic cardiac hypertrophy," and for which such various etiologies as a low potassium content of the cardiac muscle were postulated,[20] are now being designated as endomyocardial fibroelastosis.

The diagnosis of *myocarditis*, with its many etiologies and degrees of clinical significance, has been a problem to the conscientious diagnostician ever since all disorders of the myocardium, whether inflammatory or degenerative, were so labeled, and when the diagnosis of "chronic myocarditis" appeared on practically all death certificates of patients dying from heart disease. Except as it relates to rheumatic fever, diphtheria, the rickettsioses, subacute bacterial endocarditis and the post-streptococcal states, its clinical import in infectious and parasitic disease has waned. The writings of Gore and Saphir on this subject are well known.[21, 22] When associated with cardiac hypertrophy and resulting in the "chronic fibroplastic myocarditis," a striking and relentless downhill course is pursued, with death ocurring within a few months of the clinical onset.[23] This is also true of the so-called Fiedler's myocarditis in which both the immediate and ultimate prognoses are poor. These patients are subject to serious conduction defects and embolic phenomena in addition to rapid and progressive heart failure.

The entire subject of myocarditis has been ably reviewed by de la Chapelle and Kossmann.[24] These experienced cardiologists were able to find the clinical diagnosis of myocarditis made only 16 times among 68,000 patients discharged in 1952 from a large non-communicable disease center, of whom 14 had rheumatic fever or endocarditis; and among almost 11,500 patients admitted to a metropolitan infectious disease hospital, the diagnosis had been made clinically only once (in a patient with meningococcemia). This is a striking contrast to the estimated 10 per cent incidence of myocarditis found in patients coming to necropsy. These authors also concluded that cardiac enlargement is uncommon in myocarditis. It should be emphasized that more frequently than is probably realized, the main difference between "chronic myocarditis" and "idiopathic cardiac hypertrophy" depends upon the individual pathologist's definition and concept of the myocarditis process. Burchell has succinctly summarized the general experience as follows, "Viral myocarditis as an entity is well established but certainly is a rarity, difficult of exact etiologic substantiation, and difficult of assessment as regards the amount of histologic change to correlate with the clinical picture."[1]

Another condition was questioned in the patient herein described, namely, the so-called *"athletic heart."* Could his continued efforts in strenuous competitive sports have produced cardiac enlargement, either *per se* or along with the burden of his 60 extra pounds? Although White has stated that "an occasional, or more likely a rare person may, after some years of

excessively strenuous sport, develop an increase in heart size out of keeping with an increase in body size," he cautions that this condition has by no means been adequately established.[25] Dr. Burgess Gordon has devoted many years to the study of this problem both clinically and in the laboratory. He recently expressed his doubt that the pathological "athletic heart" even exists as a distinct clinical entity.[26] Another student of this problem, Sir Adolphe Abrahams, has also questioned whether there is valid evidence of cardiac hypertrophy in those accustomed to violent exercise.[33] After studying the electrocardiograms of 40 marathon runners, however, Winsor and Beckner state that the pattern of a slow cardiac rate and a high voltage of the QRS complexes and T-waves in either the standard or precordial leads or both with normal R/T ratios is characteristic.[34] They also found moderate enlargement of the heart by teleroentgenography in these athletes. Immediately after running, the heart size decreased and all the waves showed an increased voltage.

In 1949, Evans presented a careful report of 10 cases with serious heart disease characterized pathologically by both myocardial fibrosis and hypertrophy of the remaining myocardial fibers, and occurring in the same families.[27] The term *"familial cardiomegaly"* was coined. As a rule, the cardiomegaly was considerable and intracardiac thrombosis initiating embolism was frequent. The glycogen content of the myocardium was not significantly increased. The striking histological similarity to the myocardial fibrosis seen in Friedreich's disease, which is also familial and hereditary, caused him to consider some primary unknown factor which in this condition involves the central nervous system and in familial cardiomegaly affects the heart almost exclusively.

In a return to the discussion of the differential diagnosis of adiposity of the heart and cardiomegaly, two sources of radiographic error must be kept in mind, particularly in obese individuals. The apparent increase in the transverse diameter of the heart noted in stout people, in whom the heart tends to be placed horizontally above a high diaphragm, is a frequent source of concern. The other is the so-called triangular fat pad, usually seen several centimeters beyond the cardiac apex at the left pericardio-diaphragmatic angle.

Schlesinger and Reiner have recently redirected attention to the histologic entity of *focal myocytolysis of the heart*.[36] These lesions consist of miliary areas characterized by a loss of muscular syncytium, preservation of the stroma, absence of inflammatory reaction, and eventual fibrosis. Although fibrosis also finally occurs in miliary infarcts, the quicker coagulative necrosis and inflammation of the stroma differentiates the two conditions. In view of the many dissimilar conditions in which these lesions have been found, including cardiomegaly of unknown etiology and intractable congestive failure,[37, 38] myocarditis, coronary atherosclerosis, bacterial endocarditis, scleroderma, poliomyelitis, uremia, pregnancy and the puerperium, therapeutic insulin shock, and various experimental procedures in animals, it has been suggested that this lesion constitutes the final morphologic pathway for metabolic imbalances in the heart. The latter include

ischemia, anemia, hypotension, hypoglycemia, septicemia, toxemia, heart failure, cardiac dilatation and nutritional disturbances.

It is the author's contention that clinical and pathological interest should again be directed toward the fatty heart to obtain further data concerning its actual incidence and significance. The well known correlation between the incidence of degenerative heart disease, hypertension and obesity will not be belabored, but it is apparent that many misconceptions exist concerning this relationship. For example, the theory is widely held that the obesity increases the load on the heart by enlarging the vascularity of the fatty tissue and consequently increasing the distance and peripheral resistance that the blood must overcome. Taylor, Brozek and Keys have shown the fallacy of this theory by their studies on cardiac output in which it was shown that fatness *per se* does not necessarily increase the basal cardiac output and work in proportion to the increase in surface area or oxygen consumption.[28] It is quite probable that the factors of rapid onset and the longer duration of obesity are much more important to the heart than the actual degree of obesity. This has been adequately shown to be so in the case of the liver of obese individuals by both Zelman[29] and Colwell.[30]

CONCLUSION

Attention is redirected to the problem of fatty infiltration of the heart.

A probable case of "adiposity of the heart" diagnosed clinically in a living 30 year old man is presented. His asymptomatic cardiomegaly has decreased radiographically but slightly with marked weight reduction after six months.

This condition should be suspected in patients demonstrating unexplained cardiomegaly in the presence of a recent rapid and profound weight gain and in the absence of the stigmata of the other causes of heart disease. It may be either asymptomatic or manifested by heart block and congestive heart failure.

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RESUMEN

Vuelve a llamarse la atención sobre el problema de la infiltración grasosa del corazón.

Se presenta una causa probable de la "adiposidad del corazón" diagnosticada en un hombre vivo a los 30 años de edad.

Su cardiomegalia asintomática ha decrecido radiográficamente aunque ligeramente con la marcada disminución del peso después de seis meses.

Esta condición es de sospecharse en los enfermos mostrando cardiomegalia inexplicada en presencia de un aumento rápido de peso y en ausencia de otros estigmas de afección cardiaca.

Puede ser va asintomática o ya manifiesta por bloqueo cardiaco y por insuficiencia cardiaca congestiva.

RESUME

L'auteur insiste de nouveau sur le problème de l'infiltration graisseuse du coeur.

Il rapporte un cas probable de "coeur graisseux" diagnostiqué cliniquement chez un homme âgé de 30 ans. Sa cardiomégalie asymptomatique a paru légèrement diminuer au point de vue radiologique au bout de six mois, alors qu'il accusait une perte nette de poids.

Cet état devrait être suspecté chez les malades présentant une cardiomégalie inexpliquée, en même temps que l'on note chez eux une augmentation de poids importante, rapide et récente, et tandis qu'il n'y a aucune autre manifestation qui puisse être à l'origine d'affections cardiaques. Cette atteinte du coeur peut être asymptomatique mais dans d'autres cas, elle se manifeste par l'apparition de "blocs" et d'insuffisance cardiaque.

SCHLUSSFOLGERUNG

Es wird erneut die Aufmerksamkeit gerichtet auf das Problem der fettigen Infiltration des Herzens.

Ein wahrscheinlicher Fall von "Adipositas des Herzens" wird beschrieben, der klinisch bei einem lebenden 30 Jahre alten Mann diagnostiziert wurde. Seine symptomlose Herzvergrösserung ist röntgenologisch nur wenig zurückgegangen bei einem ausgesprochenen Gewichtsverlust nach 6 Monaten.

Diesen Xustand muss man bei Kranken vermuten, die ieine unerklärliche Herzvergrösserung aufweisen, gleichzeitig mit einer jüngst erfolgten raschen und erheblichen Gewichtszunahme und beim Fehlen der Anzeichen anderer Ursachen einer Herzerkrankung. Er kann entweder symptomenlos sein oder zum Ausdruck kommen in einem Herzblock und Versagen des Herzens durch Stauung.

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COMPLETE REFERENCE LIST WILL APPEAR IN REPRINTS

One Hundred and Ten Consecutive Cases of Pulmonary Resection for Tuberculosis

A New Method of Bronchial Stump Closure

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Excisional therapy for pulmonary tuberculosis is now an established and accepted procedure. It has become a highly effective form of treatment since the advent of antibiotic therapy and as a result of greatly improved surgical and anesthetic technique.

TABLE I

INCIDENCE OF BRONCHOPLEURAL FISTULA

Authors	Year	No. Resections	No. B.P.F.'s	Per Cent
O'Brien[2]	1950	202	27	12
Monod[3]	1951	112	23	20
Berard[4]	1951	230	30	12
Overholt[1]	1952	208	6	3
Davidson[5]	1954	512	86	16
Kergin[6]	1954	200	25	12.5

A perusal of all the publications on the subject, however, reveals that the incidence of bronchopleural fistula, which is one of the most disastrous complications, appears to be high. It occurred in about 8 per cent to 10 per cent of the numerous cases of pulmonary resections for tuberculosis reported by different authors (Table I). Because of the seriousness and frequency of this complication, there are physicians, internists and surgeons alike who still hesitate in advising pulmonary resection to patients who need it.

The purpose of this paper is threefold: 1. To discuss etiological factors in connection with bronchopleural fistulae. 2. To describe a new technique of bronchial closure. 3. To report 11 consecutive cases of pulmonary resection for tuberculsis.

TABLE II

ETIOLOGICAL FACTORS OF POSTEXCISIONAL B.P.F.

A) Major Factors:
   1) Peribronchial Tuberculous Infection
   2) Technical Error

B) Minor Factors:
   1) Long Bronchial Stump
   2) Residual Space
   3) Uncovered Bronchial Suture Line

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Etiological Factors

The causative factors of postexcisional bronchopleural fistula have been thoroughly investigated by many authors.

Their conclusions have incriminated infection and technical error as main factors for this complication (Table II). In so doing, they have stressed two main principles of surgery: a wound heals poorly first when it is infected, second, when it is improperly sutured. In pulmonary resection for tuberculosis, the surgeon faces the added danger of an infection of tuberculous nature; technically, he has the problem of bringing together a rigid cartilagenous anterior wall and a pliable posterior membrane.

Many authors like Stemmermann[19] et al are of the opinion that the primary cause of bronchopleural fistula is the extension of a peribronchial tuberculous empyema through the bronchial stump.

TABLE III

INCIDENCE OF BRONCHOPLEURAL FISTULA WITHOUT AND WITH STREPTOMYCIN

Authors			Number of Cases	Per Cent
Bailey[21]	1949	Without	100	14
		With	100	4
Gordon[8]	1954	Without	28	50
		With	76	16
Overholt[1]	1952	Without	229	10
		With	208	2.8

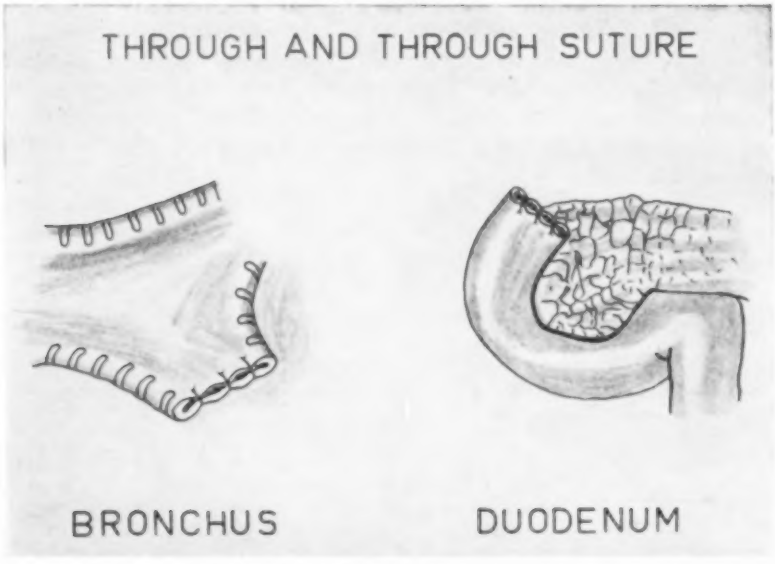

FIGURE 1

The remarkable reduction of the incidence of bronchopleural fistula since the administration of streptomycin speaks by itself (Table III). In addition, it is well known that once a patient has developed this complication, his sputum frequently turns positive for tubercle bacilli. Finally, bronchopleural fistula seldom develops following pulmonary resection performed for any disease other than tuberculosis. This peribronchial tuberculous infection may result from a contamination of the pleural cavity at time of surgery either from accidental opening of a cavity or empyema or from a time consuming technique of bronchial closure. Yet, we strongly feel that, in most instances, the peribronchial contamination takes place during the postoperative course and that it is directly induced by an improper bronchial closure.

In most of the techniques of bronchial closure now in use, the membranous and cartilagenous portions are brought together by a single row of through and through end on interrupted sutures (Figure 1). There is apposition of mucosa to mucosa which are left exposed. Any surgeon would strongly condemn such a suture performed on an intestinal wound. Still, the bronchial tree is a similar organ with a heavily contaminated lumen which in addition roofs tubercle bacilli in the case of pulmonary tuberculosis. Every suture is a wick that can bring contaminated material from the lumen into the wound. Mucosa and submucosa layers, which are heavily septic, are left exposed. In pulmonary tuberculosis, the mucosa and submucosa of the bronchus frequently show active disease.

TABLE IV

INCIDENCE OF ENDOBRONCHIAL TUBERCULOSIS IN RESECTED LUNGS

Authors	Year	No. of Cases	Per Cent
Overholt[1]	1952	437	37
Olson[7]	1953	602	40
Gordon[8]	1954	31	87
British T.B. Association[9]	1953	94	95

Microscopic studies of the resected bronchus at the line of section were performed by many authors. They reported an incidence of endobronchial tuberculosis in 37 per cent to 95 per cent of the cases (Table IV).

All these conditions favor peribronchial tuberculous empyema which leads to sloughing of the bronchial stump.

Technically, apposition of mucosa to mucosa is far from being a sound principle. Healing of the cut bronchus can only be the result of a granulation tissue formation at its end. This was shown by Reinhoff[14] as early as 1942. In addition, with through and through sutures, the shorter and more pliable membranous portion is brought down against the longer and more rigid cartilagenous portion. Then, there is marked tension on the sutures particularly dangerous on the membranous side. This may well

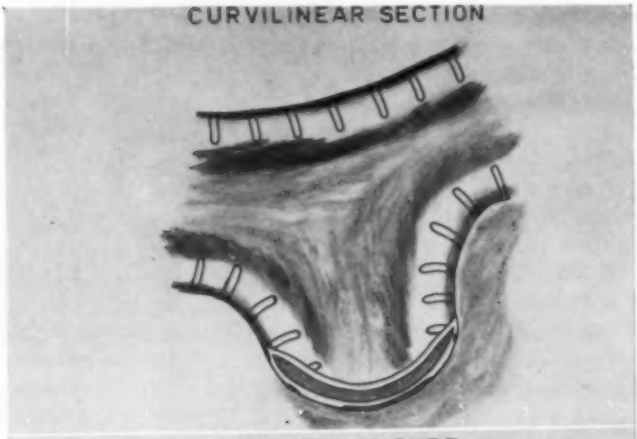

FIGURE 2

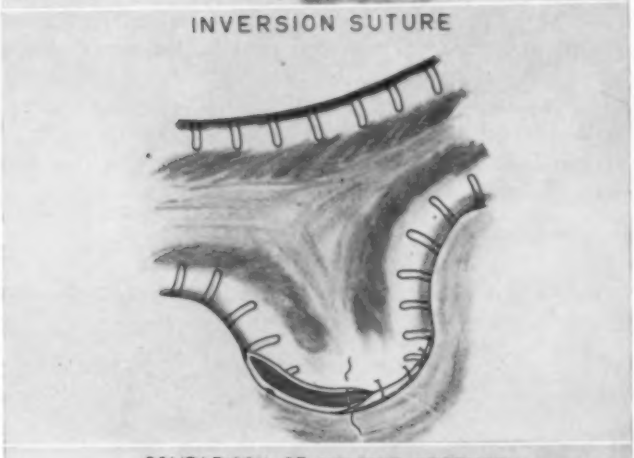

FIGURE 3

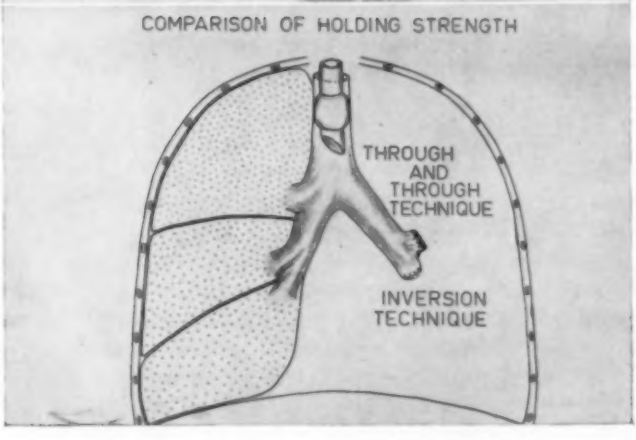

FIGURE 4

lead to necrosis, to cutting through, to leaks of air and secretions along the stitches and finally to peribronchial infection.

A short bronchial stump, a good bronchial coverage and a complete postexcisional re-expansion are belived to prevent the development of a bronchopleural fistula. It appears to us that these factors are of limited value because they cannot eliminate the hazards of a heavily septic suture line. Obviously, a short stump does not collect the amount of secretions that the pouch of a long stump would. However, as long as there are through and through sutures, the soiling of the bronchial wound by secretions moving along the stitches is far from being eliminated. It has also been reported that incomplete re-expansion following a partial resection favors the development of a bronchopleural fistula. The residual space has been referred to as a potential empyema. Indeed, it is a heavily septic suture line that has to be feared and not so much the residual space. In fact, it is not always possible for the expanding lung to fill the pleural cavity even with the best favoring measures; it is also known that bronchopleural fistula develops in spite of a well expanded lung; finally if a residual space bears such a great danger, we have quit doing pneumonectomies. Bronchial coverage by pleura, intercostal muscles, pericardial fat or adjacent connective tissues seems to afford a similar relative protection against peribronchial infection.

A New Technique of Bronchial Closure

A good technique of bronchial closure must tend to eliminate the hazards of a septic suture line without having to rely on measures of doubtful efficiency like bronchial coverage by a well expanded lung or by adjacent tissues brought over the stump. Obviously it must also promote quick healing.

The main principle of our technique is the firm approximation of the raw surfaces of the bronchial cut ends by inversion of the wound lips. It can be described as follows:

I: *Minimal Peribronchial Dissection*:

No stripping of peribronchial tissues is performed. No crushing clamp, no electric or chemical cauterization is applied proximal to the planned level of section. Blood supply to the suture line is not compromised. Devitalization and necrotic tissue formation is avoided.

II: *Curvilinear Section of the Bronchus*:

This measure insures a closure without tension on the suture line. The spring-like action of the bronchial cartilage, which normally maintains patency of the airways is eliminated. Furthermore, removal of the angular corner permits a more accurate inversion and apposition of the bronchial cut ends (Figure 2).

III: *Inversion of the Bronchial Cut Ends*:

The needle and the suture pass outside the mucosa and come out through the raw surfaces of the bronchial cut ends. When the suture is tied, the

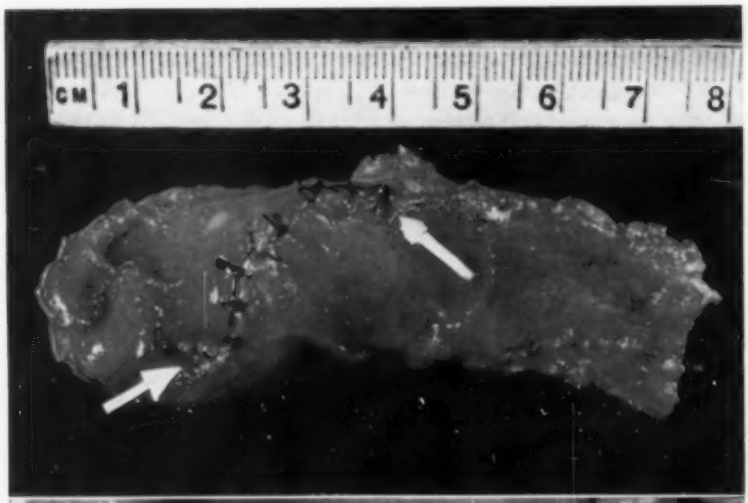

FIG. 5

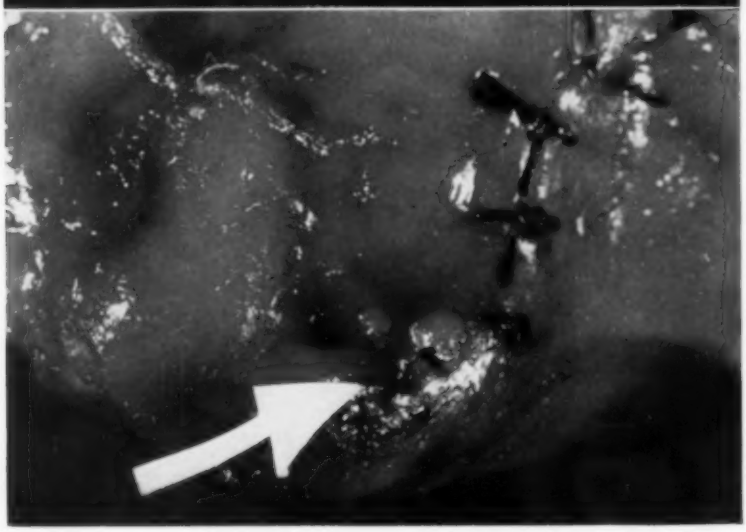

FIG. 6

cut ends invert and come into close apposition (Figure 3). The material used is multifilament nylon 3-0 or 4-0 (Zytor* or Surgilon**).

This new technique almost completely eliminates postoperative peribronchial contamination. It does not permit the mucous and submucous membranes to be exposed to the pleural cavity. As no suture material is left within the bronchial lumen, no secretion can leak through the stitch holes. Ulceration and infection are avoided. The technique is also in complete accordance with the general principles of surgery. There is a perfect

*ZYTOR: Proprietary name for multifilament nylon, Bauer & Black.
**SURGILON: Proprietary name for multifilament nylon, Davis & Gock.

alignment of the individual layers of the bronchus; quick healing is then promoted; apposition of mucosa to mucosa is avoided. Holding strength is good. This has been proved in experimental surgery on dogs.† Left upper lobe and left lower lobe lobectomies were performed on 15 dogs. With multifilament nylon 3- or 4-0, a through and through suturing technique was used on one bronchus and the inversion technique on the other (Figure 4). Then, high positive pressures were given through the endotracheal tube. At pressures ranging from 25 mm. Hg. to 40 mm. Hg. there was leakage of air and secretions through the stitch holes of the bronchus with the through and through sutures. This markedly increased at higher pressures. At pressures ranging from 115 mm. Hg. to 140 mm. Hg., bullae formation or rupture were observed in the remaining right lung. Yet, at no time did we notice leakage of air and secretions from the bronchus closed by the inversion technique. Two conclusions may be drawn from these experiences. First, with the sudden high intrabronchial pressures that develop on coughing efforts, leakage of air and secretions along through and through sutures may well occur. This may be marked during the first 48 hours postoperatively when a high negative intrathoracic pressure is maintained in the operated side by suction drainage. Second, with the inversion technique, the holding strength is good in spite of the fact that fewer stitches were needed for adequate bronchial closure.

With the inversion technique, the blood supply to the line of suture is well preserved. This is due to minimal peribronchial dissection, to the need of fewer stitches and to the fact that the lips of the bronchial wound are not held together under tension; crushing and cutting through tendency is slight. With this technique, a residual space is less likely to be a potential empyema since sepsis is little at the line of suture. If bronchial coverage is performed, it can be expected to adhere more quickly.

Results

From March 1, 1953, to March 1, 1955, we have performed 110 pulmonary resections for tuberculosis. These consecutive cases are divided in two groups.

110 PULMONARY RESECTIONS FOR TUBERCULOSIS

Type	Group I	B.P.F.	Group II	B.P.F.
Pneumonectomies	8	2	26	0
Lobectomies	9	1	31	0
Segmental Resections	2	0	28	0
Wedge	0	0	6	0
TOTAL	19	3 (15.7 Per Cent)	91	0

In the first group of 19 patients, the bronchus was closed by through and through sutures. Three patients developed bronchopleural fistula. In two, massive contamination had occurred during the surgical manoeuvers from the accidental opening of an associated tuberculous empyema. One

†This research work was made possibie by a grant from the National Department of Health and Welfare of Canada.

patient was re-operated on the seventh day following pneumonectomy because of air leaks. The sutures had been placed too far part. In the second group of 91 patients, the inversion suture technique was used; there was no incidence of bronchial fistula.

Not included in this series is a patient who had a right pneumonectomy for bronchogenic carcinoma. Unfortunately the patient died on the sixth postoperative day from heart failure. Bronchial stump examination revealed that at this early stage there was already a firm cohesion of inverted bronchial cut ends with minimal granulation tissue formation (Figures 5 and 6). Microscopic examination showed that healthy tissue containing bronchial glands had already well bridged the bronchial wound (Figure 7).

SUMMARY AND CONCLUSIONS

1. Etiological factors involved in the development of postexcisional bronchopleural fistula are reviewed. As in any type of surgical wound, sloughing results from infection and improper closure.

2. An inversion technique of bronchial closure is described. The salient points are as follows:

a) Minimal peribronchial dissection. Blood supply to the line of suture is then well preserved.

b) Curvilinear section of the bronchus. This measure abolishes the spring like action of the bronchial cartilage and ensures a closure without tension on the suture line.

c) Inversion of the bronchial cut ends. The needle and the suture pass outside the mucosa and come out through the cut ends of the bronchus.

FIGURE 7

When the suture is tied, the cut ends invert and come into close apposition.

3. With this method:

a) The septic surface of the bronchial cut ends is not exposed, eliminating possible infection during the postoperative period.

b) There is perfect alignment of the individual layers of the bronchus; quick healing is then promoted; apposition of mucosa to mucosa is avoided.

c) Holding strength of the suture is three times greater than that of through and through suture techniques.

4. One hundred ten cases of pulmonary resection for tuberculosis are reported. The last 91 cases had the inversion technique with no bronchopleural fistula.

RESUMEN

1. Se revisan los factores que influyen en el desarrollo de la fístula postexcisional broncopleural. Como en cualquier tipo de cirugía el esfacelo de la herida es resultado de infección y de cierre inadecuado.

2. Se describe una técnica de inversión para el cierre bronquial cuyos puntos salientes son:

a) Mínima disección peribronquial. El aflujo sanguíneo hasta la línea de sutura en bien conservado.

b) Sección curvilínea del bronquio. Esta medida suprime la acción de resorte del cartílago bronquial y asegura un cierre sin tension de la línea de sutura.

c) Inversión de los cabos bronquiales. La aguja y el hilo pasan afuera de la mucosa y emergen a través del corte del bronquio. Cuando la sutura desata el corte se invierte y viene a oponerse con el del otro lado.

3. Con este método:

a) La superficie séptica del cabo bronquial no se expone, eliminando la posible infección durante el postoperatorio.

b) Hay un alineamiento perfecto de las capas individuales del bronquio; la curación rápida se logra así: la sobreposición mucosa sobre mucosa se evita.

c) La fuerza de contención de la sutura es tres veces mayor que la de la sutura perforante común.

4. Ciento diez casos consecutivos de resección pulmonar por tuberculosis se relatan. En los últimos 91 casos se empleó la técnica de inversión sin que apareciera fístula broncopleural.

RESUME

1. Les auteurs passent en revue les différents facteurs étiologiques responsables de la constitution de fistules broncho-pleurales après Résection pulmnaire. Comme dans toute plaie chirurgicale, la formation de l'escarre est la conséquence de l'infection et d'une mauvaise fermeture de la plaie.

2. Les auteurs décrivent un procédé de suture bronchique inversent. Les points principaux sont les suivants:

a) Dissection péribronchique minime. L'alimentation sanguine de la ligne de suture est alors parfaitement respectée.

b) Section curviligne de la bronche. Ce procédé supprime l'action d'arc tendu du cartilage bronchique et assure une fermeture sans tension sur la ligne de suture.

c) Inversion des lèvres de la plaie bronchique. L'aiguille et la suture passent à l'extérieur de la muqueuse et sortent à travers l'entaille de la bronche. Lorsque la suture est lieé, l'entaille est renversée avec apposition étroite des levres de la plaie.

3. Par cette méthode:

a) La surface septique de l'entaille bronchique n'est pas exposée, ce qui supprime les risques d'infection à la phase post opératoire.

b) Il y a un alignement parfait des diverses couches de la bronche, une cicatrisation rapide est alors obtenue: l'apposition muqueuse à muqueuse est évitée.

c) La solidité de la suture est trois fois plus grande que celle des techniques habituelles de suture.

4. 110 cas consécutifs de résection pulmonaire pour tuberculose sont rapportés. Les 91 derniers cas furent opérés suivant la technique d'inversion et ne présentèrent pas de fistule broncho-pleurale.

ZUSAMMENFASSUNG

1. Übersicht über aetiologische Faktoren, die bei der Entstehung von bronchopleuralen Fisteln nach Exzision beteiligt sind. Wie bei jeder anderen Art chirurgischer Wunden ist die Lösung des Verschlusses die Folge einer Infektion und ungeeigneter Wundnaht.

2. Beschreibung einer Umstülpungstechnik des Bronchialverschlusses. Die entscheidenden Punkte sind folgende:

a) Minimale peribronchiale Zertrennung. Die Blutzuführung der Nahtstelle bleibt dann wohl gewahrt.

b) Gerade gebogene Durchtrennung des Bronchus. Dieses Vorgehen hebt die Federartige Wirkung des Bronchialknorpels auf un stellt einen Verschluss ohne Spanning an der Nahtlinie sicher.

c) Einstülpung der bronchialen Wundenden. Die Nadel und die Naht gehen aussen an der Schleimhaut vorbei und kommen an dem durchschnittenen Ende des Bronchus heraus. Sobald die Naht geknüpft ist, stülpen sich die Wundenden ein und lagern sich dicht an einander.

3. Mit dieser Methode:

a) Wird die septische Oberfläche der bronchialen Schnittwunde nicht exponiert und dadurch eine mögliche Infektion im Verlauf der postoperativen Phase ausgeschaltet.

b) Besteht eine vollkommene Angliechung der einzelnen Schichten des Bronchus; eine schnelle Heilung wird damit begünstigt. Eine Auflagerung von mucosa auf mucosa wird vermieden.

c) Ist das Haltevermögen der Naht dreimal grösser als dasjenige mit Techniken mit durch und durchgehender Naht.

4. Über mo aufeinander folgende Fälle von Lungenresektion bei Tuberkulose wird berichtet. Bei den letzten einundneuzig Fällen war die Ein-

stülpunkstechnik angewandt worden, ohne dass eine innere Fistel aufgetreten wäre.

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Case Report Section

Chondrosarcoma of the Posterior Mediastinum

A Case Simulating a Neurofibroma

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Mediastinal tumors are rare, but the number has increased during the past decade due to the large number of routine roentgenologic examinations of the chest, improvement in chest examinations, and progress in thoracic surgery.

The most common neoplasm of the posterior mediastinum is the neurogenic group of tumors. Neurofibromata as typical of this group often occur as round or oval-shaped next to the paravertebral gutter. When extension through an intervertebral foramen has occurred, the appearance may be that of an hour-glass or a dumbbell. Chondrosarcoma in any part of the mediastinum is rare. It is particularly unusual in the posterior mediastinum and is a unique tumor in the dumbbell variety. Such a case is that reported.

Few cases of chondrosarcoma of the mediastinum are gleaned from the literature. In 1929, Heuer[1] described a case of the posterior mediastinum involving the spinal cord reported by Elsberg. A discussion and review of anterior and posterior mediastinal tumors by Harrington[2, 3] in 1930 and 1935 did not include any chondrosarcomas. Heuer and Andrus[4] in 1940 described two chondromatous tumors occurring in the posterior mediastinum, one being hour-glass in type and causing spinal cord compression. A case of huge chondrosarcoma arising from the chest wall, probably from a benign chondroma, and extending into the thorax and abdomen was presented by Harper[5] in 1942. Six chondrosarcomas were found among 42 malignant mediastinal tumors (excluding lymphomas and metastatic tumors) by Uhrich[6] at Mayo Clinic in 1947. A primary chondrosarcoma of the lung was reported by Lowell and Tuhy[7] in 1949.

A very interesting case of chondrosarcoma of the posterior mediastinum in a 40 year old white farmer with an hour-glass involvement of the spinal canal, reported by Weisel and Ross[8] in 1950, was resected with survival. A 48 year old white woman with an anterior mediastinal chondromyxosarcoma, reported by Schwinger and Hemley[9] in 1953, had an inoperable mass which extended into and along the pulmonary artery.

Case Report: R. T. September 15, 1952. The patient is a 34 year old white male married salesman who was admitted to the hospital with the chief complaint of a burning and tingling sensation over the left shoulder and arm. This had not been severe at any time but had become more noticeable during the past three to six weeks. There had been a burning sensation over the left subscapular area intermittently for the past five years, he thinks. At times, he thought that he did not sweat as much on the left side of the chest. About four years ago, he had noted a swelling of the left side of the chest lasting about six weeks. There had been no weight loss, dysphagia, or dyspnea. Review of the systems was negative. Past history was non-contributory.

An x-ray film of the chest one year ago and four months ago were negative.

Family history revealed no familial disease.

Physical examination revealed a well-developed, well-nourished strong cooperative, intelligent white male in no apparent distress. Temperature was 98.6 degrees, pulse

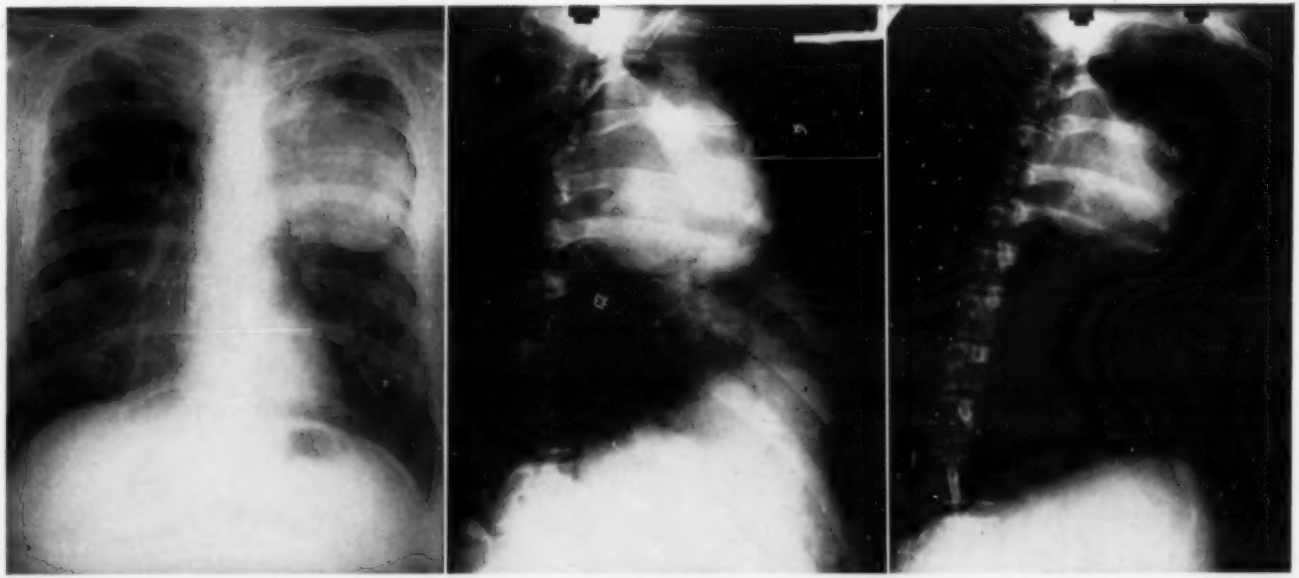

FIGURE 1 FIGURE 2 FIGURE 3

Figure 1: Anteroposterior x-ray film of chest showing a large oval-shaped shadow in the left upper posterior chest.—*Figure 2:* Lateral view of chest film showing the tumor to be situated near the dorsal spine in the posterior mediastinum.—*Figure 3:* X-ray film of dorsal spine showing suspected origin of tumor near the dorsal spine.

80, respiration 20. Blood pressure was 130/80. Skin was clear. The eye, ear, nose and throat examination was negative. The neck was normal. There were no palpable lymph nodes. The trachea was not deviated. Examination of the thorax showed good expansion, slight dullness to percussion over the posterior chest near the left subscapular area adjoining the spine. Breath sounds were normal. No rales were audible. The heart was normal in size, rate, and rhythm. Examination of the abdomen revealed no palpable organs, distension, or tenderness. The genitalia, rectal examination and extremities were normal. Neurological examination including sensations over the thorax was negative.

Complete blood counts, sedimentation rate, fasting blood sugar, non-protein nitrogen, VRDL test, liver function tests including the alkaline phosphatase test, and urinalysis were normal. A tuberculin test 1:1000 and a histoplasmin test were negative. An electrocardiogram was normal.

X-ray films of the chest, antero-posterior view (Figure 1), lateral views (Figure 2), and the dorsal spine (Figure 3) revealed a large oval-shaped well-circumscribed lobulated shadow in the left upper chest posteriorly at the level of the fourth, fifth, and sixth dorsal vertebrae extending to the spine where there is erosion of the posterior aspect of the fourth and fifth ribs and the lateral borders of the fourth and fifth dorsal vertebrae, and particularly the pedicle of the fifth. This is most likely a neurofibroma with probable intraspinal involvement at the level of the fifth dorsal vertebra.

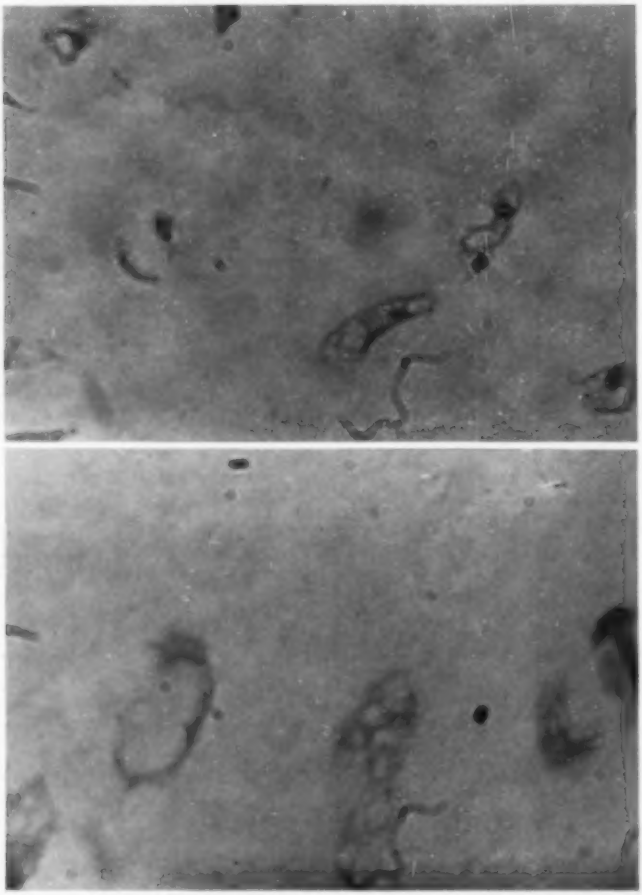

FIG. 4A

FIG. 4B

Figure 4, A and B: Photomicrographs of biopsy specimen showing predominant cartilagenous tissue with undifferentiated fibroplastic elements. × 970 magnification.

The impression by three radiologists was that the patient probably had a neurofibroma on the basis of the dumbbell appearance and its position near the paravertebral area. A consultant neurosurgeon felt that the tumor was a neurofibroma but that a chest surgeon should perform an exploratory thoracotomy. This was done by Dr. Robert McCracken.

On September 17, 1952, under endotracheal anesthesia with the patient in the lateral position, a posterolateral incision was made over the sixth rib. This rib was resected subperiosteally from the transverse process to the anterior axillary line. Small segments of the fifth and seventh ribs were also resected. The pleural cavity was entered through the bed of the sixth rib. A large, hard tumor mass, measuring about 16 to 18 centimeters in diameter, was found in the posterior mediastinum at this level. The mass was densely adherent to the lower lobe posteriorly, extending around the mediastinum to the arch of the aorta. There was a large mass on the aortic arch. There was some destruction of the fifth and sixth ribs posteriorly. Portions of the tumor were removed for sections. It was felt that the case was inoperable and the chest was closed.

Gross pathology revealed three specimens. Fragments of ribs showed erosion but no infiltration. The tumor tissue was white and firm. On cut section, this tissue was uniform and showed a cartilagenous consistency.

Microscopic examination (Figure 4) revealed variations of a basically similar pattern. Most of the tissue was cartilagenous, much of which was immature or abnormal. The cells were bizarre in appearance and disorderly in arrangement. Some areas showed osteoid tissue in irregular masses surrounded by osteoblasts. Other areas showed undifferentiated fibroplastic elements where vascular spaces were prominent. There was disagreement among the pathologists as to whether to call the tumor an osteogenic sarcoma or chondrosarcoma, the latter being finally accepted.

The post-operative course in the hospital was uneventful. Upon discharge, 1600 r units were administered over the left anterior thorax and 1400 r units over the left posterior thorax. On October 16, 1952, he was started on 1,000,000 volt deep x-ray therapy.

There was a gradual downhill course. On February 27, 1953, roentgenogram of the chest revealed a homogeneous density over the entire left lung, shift of the heart to the right, a large metastatic nodule in the right base and several smaller ones in the right upper lung. There was a small amount of fluid in the right costophrenic angle. There were metastases to the ninth right rib posteriorly.

During this time there was progressive anemia requiring several transfusions, much weight loss, and the requirement of large amounts of opiates for pain. No fluid could be aspirated at any time. The patient expired March 24, 1953.

SUMMARY

There was no means of a preoperative diagnosis of this case of chondrosarcoma of the posterior mediastinum with symptoms and roentgenologic appearance of a dumbbell neurofibroma. The close proximity to the paravertebral gutter and the paresthesias experienced would make the diagnosis of a neurogenic tumor plausible.

There was indecision among the pathologists as to whether to call this tumor an osteogenic sarcoma or a chondrosarcoma. Since the cartilagenous tissue was much more abundant, the latter diagnosis was accepted.

The finding of any mediastinal tumor is important because they have a tendency to malignant changes and may compress the thoracic viscera. The majority of such neoplasms are malignant or potentially so.

RESUMEN

No hubo medios para hacer un diagnóstico preoperatorio en este condrosarcoma del mediastino posterior con síntomas y aspecto radiológico de un neurofibroma en forma de mancuernas. La proximidad acentuada al canal paravertebral y las parestesias harían posible el diagnóstico de un tumor neurogénico.

Hubo indecisión entre los patólogos respecto de si se podría llamar a este tumor un sarcomaosteogénico o condrosarcoma.

Puesto que el tejido cartilaginoso era más abundante, esteúltimo diagnóstico fué aceptado.

El hallazgo de cualquier tumor mediastinal es importante porque tienen tendencia maligna y pueden comprimir las vísceras torácicas. La mayoría de tales neoplasmas son malignos o potencialmente malignos.

RESUME

Il n'y eut aucun moyen de faire le diagnostic préopératoire de ce cas de chondrosarcome du médiastin postérieur, dont les symptômes et l'apparence radiologique étaient d'un neurofibrome en haltères. La très grande proximité de la gouttière paravertébrale et les paresthésies mises en évidence rendaient plausible de diagnostic de tumeur neurogène.

Les anatomo-pathologistes hésitèrent à désigner cette tumeur sous le terme de sarcome ostéogénique ou de chondrosarcome. La prédominance nette du tissu cartilagineux amena à pencher pour ce dernier diagnostic.

Toute constatation de tumeur médiastinale est importante, parce que de telles tumeurs ont tendance à l'envahissement, et peuvent comprimer les viscères thoraciques. Ces tumeurs dans leur majorité sont malignes ou ont un potentiel évolutif malin.

ZUSAMMENFASSUNG

Es gab keine Möglichkeit einer praeoperativen Diagnose dieses Falles von Chondrosarcom des hinteren Mediastinums mit den Symptomen und dem röntgenologischen Aussehen eines hantelförmigen Neurofibroms. Die enge Nachbarschaft zum paravertebralen Winkel und die durchgemachten Paraesthesien machten die Diagnose eines neurogenen Tumors plausibel.

Es bestand unentschlossenheit unter den Pathologen, ob dieser Tumor als ein osteogenes Sarcom oder als ein Chondrosarcom zu bezeichnen sei. Da das knorpelbildende Gewebe bei weitem überwog, wurde die letztgenannte Diagnose angenommen.

Der Befund eines jeden Mediastinal-Tumors ist von Wichtigkeit, weil sie die Tendenz zu malignen Veränderungen haben und die thorakalen Eingeweide komprimieren können. Die Mehrheit solcher Neubildungen ist bösartig oder hat die Fähigkeit dazu.

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An Anomalous Tracheal Bronchus to the Right Upper Lobe

REPORT OF TWO CASES

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Okayama, Japan

As a result of advances in thoracic surgery, especially the rapid development of resection therapy for pulmonary tuberculosis, anomalies of the bronchial tree are being found with increasing frequency. Bronchial anomalies have now ceased to be only of academic interest to the thoracic surgeon. It is our purpose to report two cases, because relatively few reports in the literature are found on this subject.

Case Reports

Case 1: N. K., a 27 year old man, was admitted to the Ritsurin Hospital on July 25, 1953, with the complaints of fever, cough and a lot of sputum of one month duration. A chest roentgenogram revealed dense consolidation in the middle field of the right lung which was confirmed in the lateral roentgenogram. The middle lobe was entirely involved by inflammation. After ineffective antibiotic therapy, resection of the middle lobe was attempted on October 21, 1953. The upper and middle lobes were found to be firmly adherent to the anterior chest wall and no interlobar fissure was noted. There were many enlarged lymph nodes in the hilum.

From the technical point of view it was considered difficult to resect the middle lobe alone and so upper and middle lobe lobectomies *en bloc* was decided upon. Shortly after the dissection was begun at the hilum, a small cord-like bronchus supplying a portion of the right upper lobe was found below the azygos vein. After this bronchus was divided, another big bronchus which is of the same size as a normal right upper lobe bronchus and which gave off its normal branches was found about 1 cm. below the former (previously divided bronchus). It was difficult to divide this bronchus and the arteries at their stem, so they were dissected further and divided at the peripheral part of each branch. The middle lobe arteries and bronchus were divided at their stems and finally the upper and middle lobe veins divided as a whole, the upper and middle lobes were removed en bloc. Before closing the chest, it was confirmed that the anomalous bronchus arose 1 cm. above the carina.

The anomalous bronchus (Figure 1), is 0.7 cm. in diameter and it supplied a small segment of the apical anterior portion of the right upper lobe and apparently presented the arborization normally found with other bronchi. The three normal branches of the right upper bronchus gave off the normal three subdivisions.

Case 2: S. T., a 30 year old man, was diagnosed as having pulmonary tuberculosis on August, 1951, and was admitted to the Okayama City Sanatorium on October 1, 1955. A chest roentgenogram revealed few small nodules in the subclavicular region of the right upper lobe. As part of the preoperative preparation for a proposed segmental resection of the right upper lobe, bronchoscopy and bronchography were performed on October 17, 1955.

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No marked change was found on bronchoscopy. Bronchography following bronchoscopy revealed an anomalous accessory bronchus arising from the right wall of the trachea and supplying the apical portion of the right upper lobe (Figures 2 and 3). The major right upper lobe bronchus occupied its normal position and gave off two, instead of three, branches which supplied the posterior and anterior portion of the right upper lobe respectively. To confirm this finding, bronchoscopy and bronchography were repeated on November 14, 1955. This time on bronchoscopy, a small orifice of the anomalous accessory bronchus was found on the right tracheal wall 1 cm. above the carina. However, the oil failed to enter this anomalous bronchus although the two branches of the major upper lobe bronchus supplying the posterior and anterior segments were clearly demonstrated.

Apical segmental resection of the right upper lobe was done on November 29, 1955. At operation, an anomalous tracheal bronchus was found below the azygos vein and a major upper lobe bronchus was found running parallel and 1.5 cm. below the former. It was confirmed that the former supplied the apical segment and the latter the posterior and anterior segments, respectively.

COMMENT

Foster-Carter[1] classified bronchial anomalies as follows:

1) Supernumerary bronchus; 2) displaced bronchus (the bronchi are normal in number but anomalous in position); 3) congenital cystic disease.

The first case reported by the authors is classified as a case of super-

FIGURE 1: Specimen of resected upper and middle lobes showing supernumerary bronchus (Broken arrow) and three segmental branches of the right upper lobe bronchus [arrows] (Case 2).

numerary bronchus. Brock[2] described four cases of supernumerary bronchus, three of which were seen on lung dissection and the other was found by bronchography. Gerson and Rothstein[3] reported a case of supernumerary bronchus found by bronchography. Overholt and Langer,[4] and also Jackson[5] briefly mentioned the existence of anomalous tracheal bronchus, but described no details. McEwen[6] also reported a probable case of supernumerary bronchus.

In Japan, Kozu[7] reported a case found at autopsy and Kato[8] a case found by bronchography.

The second case is classified by Foster-Carter[1] as displaced bronchus. According to Gerson and Rothstein,[3] the case reported by Monk[9] as a case of an anomalous tracheal bronchus seems to be an example of this type of anomaly. Compared to the few reports in other countries, about 10 cases of this sort of anomaly have been reported in the Japanese literature.

In this anomaly, the tracheal bronchus usually supplies the apical segment alone or both apical and posterior segments as is in most cases, except in one case reported by Takeuchi[10] where the anomalous tracheal bronchus supplied the apical and anterior segments.

As far as the incidence of anomalous tracheal bronchus is concerned, no definite and reliable statistics are found. Iketani[2] stated that he has found one case of this type of anomaly in 400 bronchograms (0.25 per cent). Kato[8] found four cases of this anomaly out of a total of 725 cases, of which 115 were autopsy specimens, 110 surgically resected specimens and 500 bronchograms. Irikura[12] gave a figure of 0.6 per cent (2 cases in 320 segmental resections), Sato[13] 0.3 per cent (2 cases in 657 planigrams)

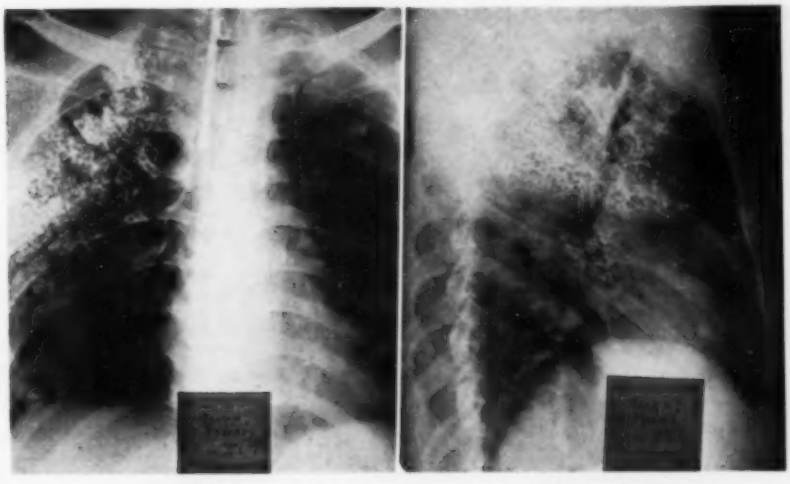

FIGURE 2 FIGURE 3

Figure 2: Antero-posterior bronchogram showing an anomalous tracheal bronchus (Case 2).—*Figure 3:* Lateral Bronchogram (Case 2).

and Takeuchi[10] 0.1 per cent (2 cases in 1100 bronchoscopies and 700 bronchograms).

It is the belief of the authors that displaced bronchi are more commonly found than supernumerary bronchi and that these anomalies are more common than shown by the statistical figures mentioned above because it could be overlooked on bronchoscopy or undiscovered by bronchography should oil fail to enter this anomalous bronchus just as happened in the present report.

Despite the presence of the anomalous tracheal bronchus, no marked variations from the usual pattern of distribution of the branches of the pulmonary artery to the corresponding bronchopulmonary segments were noted. There was only one detailed report by Monk in this regard that could be found in the literature. We would like to point out only that in our two cases, the azygos vein was always located above the anomalous bronchus, where under normal condition it is usually located above the right upper lobe bronchus.

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New Mexico Field Tuberculosis Study Program*

Interim Progress Report

This report includes a tabulation of the number of children, whose ages range from three months to fourteen years, in the various communities in this area who have been or will be included in the program.

Those listed in Group I have been registered, tuberculin tested, weighed, and therapy commenced as of June 30th.

Those listed in Group II will have had their preliminary examinations completed and therapy initiated as of December 31st.

The second examination of the children in both groups will be done after therapy has been carried on for four months and the examinations will be repeated every four months thereafter until the children have been observed for two years after completion of the year's therapy.

The response of the Indian people has been good, and no untoward results of the therapy program have been noted.

An interesting sidelight of the program: Alamo and Ramah Navajo communities have long been suspected of having a high incidence of tuberculosis and special care of the children who presented evidence of poor health has been going on for several years. Skin tests for brucellosis and coccidiomycosis were performed in addition to the tuberculin tests, at the two Navajo communities and, for the purposes of comparison, at McCartys where the sheep and goat economy was the main source of livelihood:

Pueblo		Per Cent Pos. Tuberculin	Per Cent Pos. Brucellergin
Alamo	Navajo	7.9	37.5
Ramah	Navajo	8.5	21.8
McCartys	Pueblo (Acomita)	5.5	3.8

The public health problem thus discovered is being made a matter of investigation by the Public Health Service and the Department of Agriculture. No evidence of coccidiomycosis was found at Alamo.

*Sponsored by the Committee on Indian Affairs, American College of Chest Physicians; supported by a grant from the Department of Health, Education, and Welfare, Public Health Service, supervised by the University of Pennsylvania School of Medicine.

Pueblo	Number Tested	Number Positive	Per Cent Positive
GROUP I			
TOTAL	1,988	236	11.9
Encinal	29	0	0.0
Nambe	24	0	0.0
Taos	110	2	1.8
Old Laguna	137	4	2.8
Santa Clara	96	2	3.1
Picuris	30	1	3.3
Paraje	61	2	3.2
Tesuque	22	1	4.5
Mesita	74	5	6.7
Santa Anna	84	7	7.5
Seama	66	5	7.6
Paquate	38	3	7.8
San Felipe	192	15	7.8
Alamo (Navajo)	64	5	7.9
San Ildefonso	80	7	8.7
San Juan	106	15	14.1
Santo Domingo	314	57	15.0
Zia	122	23	18.8
Jemez	205	39	19.0
Cochiti	82	18	22.2
Canoncito	52	25	48.1
GROUP II			
TOTAL (to date)	2,147	224	10.5
Acomita	256	14	5.5
Zuni	965	108	11.4
Mescalero (Apache)	146	11	7.5
Ramah (Navajo)	164	14	8.5
Towoac (Ute Mountain)	99	22	22.3
Ignacio (Southern Ute)	197	29	14.7
Jicarilla (Apache)	320	26	8.1
Albuquerque Indian School	312*		
Santa Fe Indian School	137*		
St. Catherine Mission School	65*		
Isleta	206*		
Sandia	25*		
TOTAL Program	4,880		

*Not tested, but will be included in the Program.

Arthur W. Dahlstrom, M.D., *Chairman*
Committee on Indian Affairs

Editorial

THE FOURTH INTERNATIONAL CONGRESS

International congresses in the field of medicine are born out of a desire to constitute a free forum for the mutual exchange of scientific data, new discoveries and useful professional information pertaining to the diagnosis, treatment and prevention of ailments. Measured by this standard, the Congress held in Cologne, Germany, in August 1956 fulfills all the ideals for which its sponsor, the American College of Chest Physicians, has been striving for a good many years.

The record-breaking attendance, with registrants from all over the civilized world, attests to the significance of this convention as well as the impressive recognition the College is receiving in medical circles interested in progress.

From direct personal interviews with colleagues from the United States and from distant lands, I can say without fear of contradiction that the Congress was a huge success.

This prompts me to pay my sincere compliments, admiration and gratitude to Mr. Murray Kornfeld, Executive Director of the College, and his staff who individually and collectively contributed tremendously to make this an unforgettable event in the annals of medical history. Also, a great deal of appreciation and thanks are to be conveyed to our German colleagues who have served this cause with so much enthusiasm and devotion.

A detailed report on the salient happenings at the Congress is available to all concerned. To this, may I be permitted to add as a corollary, a brief commentary.

The number of doctors attending the Congress, the number of papers read, the news value and scientific novelty of expert contributions are of importance in assaying the merit of the Congress of Cologne. But let us not forget that meetings of this type have immeasurable intangible values. Just think of the unique opportunity of meeting face to face distinguished clinicians, outstanding research workers and eloquent teachers of medicine. Consider the rare privilege of conversing with famous men whose brilliant minds virtually radiate new inspiration and are capable of setting up a chain reaction of creative thoughts.

It was my good fortune, as Chairman of the Council on International Affairs, to do my modest share in the planning, preparation and organization of this Congress. Its unprecedented success is the best proof that it was a most worthwhile endeavor.

Like an artisan finishing a precious creation, I went to this Congress with much trepidation. But the events attested to the soundness of our hopes, expectations and ideals. As all of my colleagues, I have learned very much. And what I learned was not all medical science. Above all, I learned that in the glow of true scientific interest no virus of nationalistic prejudice survives.

Andrew L. Banyai, M.D., Chairman
Council on International Affairs

The President's Page

To the Members of the American College of Chest Physicians:

May I first take this opportunity to wish all of you a very happy and successful New Year. I should like to express to you my sincere thanks and deep appreciation of the honor that you have conferred on me in electing me as your President. It is my earnest hope that I may prove worthy of your trust.

The past year has been a most satisfactory one for the College. All of its medical meetings have been well attended and the programs that have been presented have been well received. The zest and enthusiasm with which the members have participated in the various committee meetings and the panel and round table discussions have been most stimulating. All this speaks well for the future of the College. The increasing number of young members who are taking an active part in, and accepting the responsibility for, the organization of the scientific programs is especially gratifying and is vitally important to the success of any organization.

The Fourth International Congress on Diseases of the Chest, which was held in Cologne, Germany, in August under the sponsorship of the American College of Chest Physicians, proved to be one of the most successful medical meetings ever held. It was attended by 2,163 physicians from 58 different countries and territories throughout the world. The meeting was important not only from the scientific standpoint, but also from an international standpoint, wherein it proved to be a valuable agent for the improvement of international relations.

During the past year we have witnessed a steady increase in our membership. This has been accomplished in spite of the fact that the medical standards necessary for admission have been becoming gradually more stringent. Your College has assumed a place of paramount importance in the fight against medical ignorance and against cardiopulmonary disease.

The continued success of the postgraduate courses which are offered by the American College of Chest Physicians is worthy of comment. The fact that other medical groups are attempting to emulate these courses speaks well of their success and is the highest form of praise. Special thanks are due to Dr. Peabody and the many members of the College who have contributed so generously of their time, experience and knowledge to make these meetings a success. It is ample testimony that physicians in general, and our members in particular, are motivated by the highest ideals and the desire to advance the frontiers of medical knowledge for the betterment of mankind.

The year which lies ahead promises to be a most interesting and exciting one. There are many challenging problems that beckon for solution. The possible use of the various isotopes, endocrines and chemotherapeutic agents in the field of cardiopulmonary diseases is most alluring. Undoubtedly, many of our members will play vital roles in these studies and will report to us from time to time during the year concerning their progress. They are indeed in need of our full and hearty support. Because of the uncertain state of the world today it is no longer possible for a sizable segment of the medical profession to carry out adequate research, and our colleagues from underprivileged areas look to us more than ever before for aid, inspiration and guidance in the battle against disease. It is imperative that we do not fail them in this respect.

It is the aim of the College to improve the standards of medicine, to encourage the young men interested in medical research, and to afford the opportunity to our members for the exchange of information and ideas which may be of benefit to the care of the sick. It is the profound hope of your officers that the College may be of service to you at all times.

A. J. Morsch

INTERIM SESSION

The Interim Session of the American College of Chest Physicians was held at the Hotel Benjamin Franklin, Seattle, Washington, November 24-26, 1956. The Pacific Northwest Chapter of the College presented a scientific program on Sunday, November 25. More than 250 physicians registered for the meeting and participated in the panel discussions, round table discussions and fireside conferences. The chapter sponsored a cocktail party and dinner on Sunday evening. The dinner meeting was addressed by Dr. Herman J. Moersch, Rochester, Minnesota, President of the College, and by Mr. Murray Kornfeld, Chicago, Illinois, Executive Director.

On Saturday, November 24, the Board of Examiners conducted oral and written examinations for Fellowship in the College, and a number of committee meetings and conferences were held. The semi-annual meeting of the Board of Regents and a joint meeting of the Board of Governors and Board of Regents of the College were held on Monday, November 26.

The Clinical Meeting of the American Medical Association was held in Seattle, November 27-30. An excellent scientific program, as well as a splendid display of scientific and technical exhibits were organized for this meeting.

BOARD OF REGENTS AND BOARD OF GOVERNORS MEETINGS

The semi-annual meetings of the Board of Regents and Board of Governors of the College were held on Monday, November 26, at the Hotel Benjamin Franklin, Seattle. The following officers and guests were present:

Albert H. Andrews, Chicago, Illinois
Norman Arcese, Seattle, Washington
John F. Briggs, St. Paul, Minnesota
William S. Conklin, Portland, Oregon
James P. Cooney, Washington, D. C.
Seymour M. Farber, San Francisco, California
Carl H. Gellenthien, Valmora, New Mexico
Alfred Goldman, St. Louis, Missouri
Burgess L. Gordon, Philadelphia, Pennsylvania
Elliott Harrison, Vancouver, B. C., Canada
Howard L. Hull, Yakima, Washington
Hollis E. Johnson, Nashville, Tennessee
Edwin R. Levine, Chicago, Illinois
Gordon L. Maurice, Portland, Oregon
Donald R. McKay, Buffalo, New York
Herman J. Moersch, Rochester, Minnesota
Edward H. Morgan, Seattle, Washington
J. Arthur Myers, Minneapolis, Minnesota
John E. Nelson, Seattle, Washington
Arthur M. Olsen, Rochester, Minnesota
J. Winthrop Peabody, Washington, D. C.
Charles K. Petter, Waukegan, Illinois
William R. Rumel, Salt Lake City, Utah
Frederick Slyfield, Seattle, Washington
Frank I. Terrill, Deer Lodge, Montana
Harold G. Trimble, Oakland, California
Buford H. Wardrip, San Jose, California
Murray Kornfeld, Executive Director, Chicago, Illinois
Harriet L. Kruse, Executive Assistant, Chicago, Illinois

The joint meeting of the Board of Governors and Board of Regents of the College was held at 10 a.m. on Monday, November 26, and the semi-annual meeting of the Board of Regents was held at 2:00 p.m. Dr. Briggs, chairman of the Board of Regents, presided, and introduced the officials and guests of the College. Dr. Norman Arcese, chairman of the Committee on Arrangements for the meeting, welcomed the College members to Seattle.

Report of The Council on Postgraduate Medical Education

The Council is pleased to report that the 11th Annual Postgraduate Course on Diseases of the Chest was held in Chicago during the week of October 15-19, 1956, and that 67 physicians were enrolled. The 9th Annual Postgraduate Course on Diseases of the Chest was presented in New York City, November 12-16 with an enrollment of 96 physicians. The following postgraduate courses have been scheduled for presentation in 1957, under the sponsorship of our Council:

Nashville, Tennessee	January 14-18
San Francisco, California	February 25-March 1
Milwaukee, Wisconsin	March 6-13-20-27
Newark, New Jersey	March 6-13-20-27
Philadelphia, Pennsylvania	April 1-5
Chicago, Illinois	October 21-25
New York City	November 11-15
Los Angeles, California	December 9-13

The Council on Postgraduate Medical Education has direct responsibility for the postgraduate courses sponsored by the College, which are presented with the cooperation of the College Chapters in the respective states. The members of the staffs of the medical schools and hospitals in each area also cooperate with our Council in the presentation of these postgraduate courses.

J. Winthrop Peabody, M.D.
Chairman

Report of The Council on Undergraduate Medical Education
1957 Essay Award Contest

To date 64 requests for information and application forms have been received from students in the following medical schools in the United States:

Baylor University
College of Medical Evangelists
Harvard University
Howard University
Jefferson Medical College
Northwestern University
Ohio State University
St. Louis University
State University of New York
Temple University
University of Buffalo
University of California
University of Minnesota
University of Nebraska
University of Oregon
University of Rochester
Woman's Medical College of Pennsylvania

and also from other countries:

Argentina
Australia
Canada
East Pakistan
England
Germany
India
Italy
Lebanon
North Ireland
Philippines
Puerto Rico
South Africa
Switzerland

At the last Annual Meeting of the College held in Chicago, June 7-10, 1956, upon recommendation of the Council on Undergraduate Medical Education, the Board of Regents voted to increase the cash awards from $400 to $1,000. Accordingly, the cash awards for the contest, which will close on April 10, will be $500 for first prize, $300 for second prize, and $200 for the third prize. In addition, each winner will receive a certificate of merit.

The Council on Undergraduate Medical Education urges that members of the College affiliated with medical schools where students have not as yet entered the contest make every effort to bring this contest to the attention of the undergraduate students in their medical schools and to stimulate their interest in diseases of the chest.

Theodore H. Noehren, M.D.
Chairman

Report on Books Sponsored by the College

The American College of Chest Physicians initiated a program in 1949 of publishing books on timely subjects concerned with diseases of the chest, and invited its members to contribute chapters to the books in order that the most recent concepts in the specialty would be brought to the attention of the medical profession. Publishers of medical books have expressed an interest in this type of multiple authorship, under the guidance of the College.

In 1949, the College sponsored a book entitled *"The Fundamentals of Pulmonary Tuberculosis and Its Complications"* with Dr. Edward W. Hayes Sr., Monrovia, California, as chairman of the Editorial Committee. In 1954, the College sponsored a book entitled *"Nontuberculous Diseases of the Chest"* with Dr. Andrew L. Banyai, Milwaukee, Wisconsin, as chairman of the Editorial Committee. Both of these books were published by the Charles C Thomas Company and were well received. In November, 1956, a book entitled *"Personality, Stress and Tuberculosis"* with Dr. Phineas J. Sparer, Memphis, Tennessee, chairman of the Editorial Committee, was published by the International Universities Press.

We now have on the press a book entitled *"Clinical Cardiopulmonary Physiology."* This book is being published by Grune & Stratton. The publishers have announced that there is an advance sale of over one thousand copies and we trust that the book will be available within the next few weeks.

Going to press early in 1957, is a book entitled *"Roentgenology of the Chest,"* with Dr. Coleman B. Rabin, New York City, as chairman of the Editorial Committee. Arrangements have been made with the Charles C Thomas Company for the publication of this book. Another book, dealing with thoracic surgery, the exact title of which has not yet been agreed upon, is now ready in manuscript form and will be published under the editorship of Dr. Alfred Goldman, Los Angeles, California, in the near future.

The publication of these books under the sponsorship of the American College of Chest Physicians has given many members an opportunity to actively participate in this most worthwhile project. More than two hundred physicians have participated by contributing chapters for the books and thousands of copies have been distributed throughout the world. Most of the books have been translated into other languages. It is expected that the College will sponsor other books on subjects concerning diseases of the chest as the need arises, and we are certain that these books will enjoy the same popularity as those which have already been published.

I was fortunate to have had a part in contributing to some of these books and also to serve as chairman of the Editorial Committee for the book on *"Clinical Cardiopulmonary Physiology."* To me it has been a most stimulating experience and one in which I was very happy to participate. I trust that many of you will have the opportunity to experience this same satisfaction in contributing to or editing a College book.

Burgess L. Gordon, M.D., President-Elect
American College of Chest Physicians

Report of the Committee on Rehabilitation

It has been recommended by the committee that a program or programs of topics dealing with the various aspects of rehabilitation in pulmonary disease be organized for the purpose of study and evaluation of this problem and that the results of these studies be made available to the societies and agencies concerned with rehabilitation. That liaison with interested societies be considered upon request from such societies.

That joint meetings with the Section on Rehabilitation under the Committee on Cardiovascular Disease of the College be encouraged for overall planning in the broad field of rehabilitation in chest disease.

That the membership of this committee be increased to carry out these recommendations.

Leonard C. Evander, M.D.
Chairman

Report of the Committee on Membership

Between March 15 and September 15, 1956, 262 applications from all parts of the world were received and presented to the Board of Regents. Of these applications, 115 were for Fellowship, 62 for Associate Fellowship, 56 for Associate Membership and 29 for advancement to Fellowship. Of this group, 156 were from physicians in the United States and Canada and 106 were filed by physicians from the following countries or territories: Argentina, Austria, Brazil, Burma, Free China, Cuba, Czechoslovakia, East Pakistan, Egypt, France, Germany, Greece, Hong Kong, India, Iran, Iraq, Israel, Italy, Japan, Korea, Lebanon, Mexico, Philippines, Poland, Singapore, South Africa, Spain, Switzerland, Syria, Thailand, Turkey, Venezuela, West Pakistan and Yugoslavia.

Of the total 233 new applications presented to the Board of Regents, 5 are being held for further investigation. Eight of the physicians from the United States and Canada who applied for Fellowship were reclassified as Associate Fellows, and 3 applications for advancement to Fellowship have been tabled.

With the admission of 228 new members, the total membership of the College is now 5826. There are 65 applications for presentation to the Board of Regents at the 23rd Annual Meeting of the College in June 1957, in addition to those received between now and March 15.

Chevalier L. Jackson, M.D.
Chairman

Report of the Committee on Physiologic Therapy

The committee has been concerned with the problem of establishing a program for training inhalation therapists and upon receipt of a request from the Council on Medical Education and Hospitals of the American Medical Association for information regarding the effective organization of such a program, it was recommended that the President of the American College of Chest Physicians be authorized to request the American Society of Anesthesiology, also concerned with this problem, to appoint a committee of three members of their society to meet jointly with a similar committee of the College for the purpose of discussing this request. Upon approval of the proper bodies of both the American Society of Anesthesiology and the American College of Chest Physicians, the proposals of the joint committee will be submitted to the Council on Medical Education and Hospitals of the American Medical Association.

A resolution submitted by the Committee on Physiologic Therapy and approved by the Council on Research and the Board of Regents of the College, expressed the congratulations of the American College of Chest Physicians to the Medical College Hospital of the Medical College of South Carolina for its Institute on Inhalation Therapy, which, to the best of our knowledge, is the first medical school to conduct an Institute of Inhalation Therapy for therapists. It is the belief of the College that patients will benefit by improvement in the training and education of inhalation therapists. A copy of this resolution has been forwarded to the chairman of the division of anesthesiology of the Medical College of South Carolina.

Albert H. Andrews, M.D.
Chairman

Report of the Committee on Microbiology

This was the first meeting of the Committee on Microbiology of the American College of Chest Physicians (June 7, 1956, Chicago, Illinois). At this time, your committee is attempting to list the problems facing it, with the view to giving detailed study to each of the problems at some later date. The chief problems in this field are to study:

I. The general biology of microorganisms causing diseases of the chest, and to give recommendations for methods of culturing and identifying these organisms.

A. Mycobacterium tuberculosis:

1. Culture methods:

Your committee recommends that routine cultures for tubercle ba-

cilli be carried out on at least two tubes of each of two media. It recommends that one of those two media should be an egg medium, either Lowenstein-Jensen, or American Trudeau Society media, with a preference for the former as being the best medium for the primary isolation of tubercle bacilli. Admittedly, simplicity of preparation recommends the latter. The second medium used should be the A.T.S. medium, the blood medium of Tarshis, the medium of Saenz, or any other medium that has proven satisfactory.

For digestion of specimens, 3% NaOH is recommended, but 4% oxalic acid or 3% HCl may be used in certain circumstances. If specimens are to be mailed, however, 10% $Na_3 PO_4$ should be added to the specimen before mailing. If the specimen is such that it is sterile and has been collected aseptically (e.g. spinal and joint fluids, and sometimes pleural, pericardial and tissue fluids), it should be inoculated directly without prior digestion.

Cultures should be read at the end of two weeks, and at weekly intervals thereafter. As soon as definite growth is observed, a positive report should be submitted. If no growth is noticed at the end of six weeks, a preliminary negative report should be submitted. The tubes should be kept for another six weeks (12 weeks in all) before a final negative report is submitted.

It should be pointed out that the use of guinea pigs for primary isolation of tubercle bacilli is not infallible since many strains do not produce progressive disease in these animals, whereas they may be recovered from patients by cultural methods. This applies both to antibiotic resistant tubercle bacilli and to other atypical acid-fast organisms. The typing of organisms recovered on culture and animal inoculation is recommended, however, with techniques that can be found in standard manuals. For this purpose, not only guinea pigs, but rabbits, mice, chickens and hamsters may be desired.

2. Methods of testing resistance to antimicrobial agents:

There are two methods of testing resistance to antimicrobial agents: (1) The direct method of inoculation of sputum onto solid tube slants containing graduated doses of the required antimicrobial agent, and (2) the inoculation of the culture recovered from the patient into tubes of liquid media containing varying concentration of the antibiotic. The first method has the advantage of simplicity, a saving of the patient's time in arriving at the answer and of giving information about the comparative numbers of sensitive and resistant organisms present. The first method also has the disadvantages that about 50% of cultures from patients under treatment are negative at the present time, which means that a tremendous amount of labor is wasted with this procedure. Furthermore, much of the antibiotic may be destroyed by the inspissation which is essential if antibiotic is to be incorporated into a solid medium. The second method has the advantage that a known amount of antibiotic may be incorporated directly into the medium after autoclaving. Your committee will give further recommendations concerning this complex problem at a later date.

3. Research studies on the biology of the tubercle bacillus:

Heretofore, unidentified acid-fast bacteria have been repeatedly cultured from human secretions and tissues. These should be the subject of intensified studies by competent laboratories and should not be discarded as contaminants. Chemical, bacteriological, immunological, and animal pathogenetic studies should be conducted on this group of organisms with a view to arriving at useful methods of classification, and to determine the role these organisms may play in human disease.

B. Other bacteria that cause chest disease:

In the performance of bacteriological tests, your committee feels that all positive findings of bacteria from clinical material should be reported. Particularly should statements such as "normal flora" be condemned. It has been found increasingly in recent years that numer-

ous organisms previously considered non-pathogenic for human beings may be the inciting agents of human diseases, especially when the patient is receiving antibiotics and steroid therapy. Standard methods for identification of any such bacteria should be used.

C. Pathogenic fungi:

Fungi are being found to produce human disease with increasing frequency. It is recognized that antimicrobial and steroid therapy may enhance the virulence of certain fungi. Further progress reports on this subject will be forthcoming.

D. Animal parasites:

Your committee recognizes that animal parasites may occasionally cause chest diseases, such as Endamoeba histolytica, Echinococcus granulosus, etc., and should receive future consideration.

E. Viruses:

Recent developments in virology have been applied to diseases of the chest. Specifically, the "echo viruses" and the APC viruses have been isolated from the respiratory tract, suggesting that they may play an important role in lung disease. Your committee recommends that further investigation be done in this important field.

II. Your committee should act as a steering committee to evaluate research proposals from various individuals and institutions and help allocate donations and grants from drug houses and other sources for research studies in the various fields mentioned above.

III. Your committee should help establish training schools and encourage the training of more laboratory technicians in the various microbiological fields mentioned above.

In conclusion, your committee makes the following specific recommendations:

(1) That the committee's activities be continued;
(2) That many of the problems listed above be the subject of detailed reports at some future time;
(3) That the committee be expanded to include one or more authorities on virology;
(4) That it be a rotating committee as to chairmanship and membership, similar to other committees.

Henry C. Sweany, M.D., Chairman
Martin M. Cummings, M.D., Vice-Chairman
Oscar Auerbach, M.D.
Emil Bogen, M.D.
Michael L. Furcolow, M.D.
Ann Pollak, M.D.

Dr. Myers, chairman of the Editorial Board of the College Journal, *Diseases of the Chest*, announced that in January, 1957, the circulation of the journal would reach 8,000 copies monthly, covering 88 countries and territories throughout the world. There has also been an increase in the number of advertising pages in the journal, Dr. Myers stated.

Dr. Andrews presented a resolution to authorize the establishment of a Resident Loan Fund for the purpose of giving financial assistance to residents in furthering their training in diseases of the chest. It was requested that the College contribute the sum of $10,000 to start the fund. The resolution was adopted unanimously and it was recommended that the President appoint a committee to study the mechanics of establishing and administering this fund.

Dr. Moersch recommended that the responsibility of selecting the recipients of the College Medal be placed with the Executive Council of the College. Upon motion, duly seconded, this recommendation was unanimously accepted.

The following recommendations for the establishment of new committees were accepted unanimously by the Board:

"Committee on Nomenclature in Cardiopulmonary Physiology"
"Committee on Pulmonary Diseases in Children"

It was further recommended that these committees meet jointly at the annual meetings of the College with the Committee on Physiologic Therapy and the Section on Pediatric Cardiology, respectively.

It was announced that the 23rd Annual Meeting of the College would be held at the Commodore Hotel, New York City, May 29-June 2, 1957.

College Chapter News

NEW YORK STATE CHAPTER

The 17th Annual Clinical Meeting of the New York State Chapter will be held at the Park-Sheraton Hotel, New York City, February 22-23. Dr. Irving Kroop, Brooklyn, has arranged the following scientific program:

FEBRUARY 22

9:00 a.m. Motion Picture—"Ether Analgesia for Cardiac Surgery"
Joseph F. Artusio, Jr., New York City
Motion Picture—"Glossopharyngeal Breathing"
Hondo Respiratory Center for Poliomyelitis, California
"The Log Egram"
Elmer St. John, Binghamton, New York
Discussion: Solomon Schwartz, Brooklyn, New York
"Final Step in the Rehabilitation of the Cavernostomized Patient"
E. E. Rockey, New York City
Discussion: Philip Crastnopol, Brooklyn, New York
"Evaluation of Dyspnea in Pulmonary Emphysema by Application of Therapeutic Procedures"
Alvan L. Barach, New York City
Discussion: Harold A. Lyons, Brooklyn, New York

12:00 noon Luncheon—"A Classification of Persons with Mitral Stenosis as a Guide to Therapy"
Guest Speaker: Louis A. Soloff, Philadelphia, Pennsylvania
Discussion: Charles K. Friedberg, New York City

2:00 p.m. "Stumping the Experts" (Panel)
Moderator: David Spain, Brooklyn, New York
"Surgery of the Thoracic Aorta"
Allan Stranahan, Albany, New York
Discussion: Alvin A. Bakst, Brooklyn, New York
"Carcinoma of the Lung Simulating Other Pulmonary Disease"
Harry H. Epstein, Manhattan Beach, New York
Discussion: Edgar P. Mannix, Jr., Brooklyn, New York

FEBRUARY 23

This session will be held at the Nathan B. Van Etten Hospital, Albert Einstein College of Medicine, Yeshiva University, Bronx. Bus transportation will be provided from the Park-Sheraton Hotel.
Chairman: Eli H. Rubin, Bronx

10:00 a.m. "Diseases Affecting the Lesser Circulation"
1. Physiologic Considerations—Charles W. Frank
2. Cardiac Manifestations—Abraham Jezer
3. Pulmonary Manifestations—Eli H. Rubin
4. Surgical Implications—Charles Ripstein

"Clinical-Pathological Conference"
Alfred A. Angrist, New York City, Moderator

12:30 p.m. Luncheon (complimentary)

INDIANA CHAPTER

Members of the Indiana Chapter elected the following new officers at a meeting on October 17:

President:	Donald W. Brodie, Indianapolis
Vice-President:	George S. Bond, Indianapolis
Secretary-Treasurer:	Donald F. MacLeod, Morocco

PACIFIC NORTHWEST CHAPTER

The annual meeting of the Pacific Northwest Chapter was held in Seattle on November 25, in conjunction with the Interim Session of the College. Chapter officers elected for the coming year are as follows:

President:	Gordon L. Maurice, Portland, Oregon
Vice-President:	William G. Trapp, Vancouver, B. C., Canada
Secretary-Treasurer:	Peter J. Galante, Portland, Oregon

SOUTHERN CHAPTER

The Southern Chapter met jointly with the Potomac Chapter at the Shoreham Hotel, Washington, D. C., November 11-12. The Third Paul Turner Lecture was presented by Dr. O. Theron Clagett, Rochester, Minnesota. The following officers of the Southern Chapter were elected:

President:	Robert E. Schwartz, Hattiesburg, Mississippi
1st Vice-President:	Joe S. Cruise, Atlanta, Georgia
2nd Vice-President:	Daniel E. Jenkins, Houston, Texas
Secretary-Treasurer:	A. J. Steiner, St. Louis, Missouri

Members of the Potomac Chapter voted to retain their present officers.

HONG KONG AND CHINA CHAPTER

A joint meeting of the Hong Kong and China Chapter of the College and the Hong Kong Branch of the British Institute of Radiology was held at the Ruttonjee Sanatorium, Hong Kong, October 18. Following a business meeting at which Dr. H. C. Ho presided, Drs. Mary Aquinas, Mary Gabriel, T. P. Wu, H. C. Ho and Alan Chan presented x-rays dealing with chest disease which were discussed by the group attending the meeting.

NEWS NOTES

Dr. Andre F. Cournand, New York City, and **Dr. Werner Forssmann**, Bad Kreuznach, Germany, Fellows of the College, were awarded the 1957 Nobel Prize in Medicine, together with **Dr. Dickinson W. Richards**, New York City.

Dr. Sidney N. Gellis, formerly Chief of the Tuberculosis Section, VA Hospital, Tucson, Arizona, has joined the research staff of Eli Lilly and Company, Indianapolis, Indiana. Dr. Gellis will be associated with the Department of Medical Administration and will conduct clinical research in the field of tuberculosis.

Colonel Eugene C. Jacobs, MC, commanding officer of the Army Hospital at Fort Monroe, Virginia, received the Sir Henry Wellcome Medal and Prize recently for the best essay on a military medical subject. Colonel Jacobs' essay is entitled, "Tuberculosis: Yet an Unconquered Disease."

INTERNATIONAL MEDICAL FILM PROGRAM

The international medical film program, new feature of the American Medical Association's 1957 annual meeting, has been announced by Mr. Ralph Creer, Director of Motion Pictures and Medical Television, American Medical Association. The aim of the film program is to bring before the doctors attending the meeting outstanding motion pictures produced in other countries dealing with many aspects of medical science. Although the film program is in no way competitive, a certificate of participation will be awarded to each film of distinction selected for showing. The program will be presented at the Barbizon Plaza Hotel, New York City, June 3-7, 1957. Applications for the program and further information can be obtained from the American Medical Association, Motion Pictures and Medical Television, 535 North Dearborn Street, Chicago 10, Illinois, U. S. A.

ANNOUNCEMENT

The Sixth Biennial Postgraduate Course on Diseases of the Chest, co-sponsored by the Los Angeles County Tuberculosis and Health Association and the Los Angeles County Medical Association's Section on Diseases of the Chest, will be given on January 31, February 1 and 2 in Los Angeles. Further information and advance registration may be obtained by writing to: David Salkin, M.D., 1670 Beverly Boulevard, Los Angeles 26, California.

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POSITIONS AVAILABLE

Assistant Medical Director wanted for approved chest disease hospital. Must have, or be able to aequire, California license. Clinical and research experience in pulmonary diseases desired. Administrative background not essential. Salary $11,000. Please address inquiries to Box 288A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Associate physician wanted for approved chest disease hospital, with at least one year's training in pulmonary diseases. Must have or be able to acquire California license. Salary $9,600. Please address inquiries to Box 289A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Physician wanted to develop pulmonary function laboratory in chest disease hospital. Salary $12,000. Please supply full details of experience and qualifications in original letter. Please address inquiries to Box 290A, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

Associate Medical Director wanted for 100-bed tuberculosis hospital. North American graduate, salary $8,500-$9,500, complete maintenance. Apply Medical Director and Superintendent, District 1 Tuberculosis Hospital, Madisonville, Kentucky, or State Tuberculosis Hospital Commission, New State Office Building, Frankfort, Kentucky.

Medical Director wanted for 150-bed tuberculosis hospital in Seward, Alaska. Salary $15,000 per annum, plus maintenance. For details, write Paul W. Nelson, M.H.A., Administrator, or F. J. Phillips, M.D., F.A.C.S., Medical Director and Thoracic Surgeon, Seward Sanatorium, Bartlett, Alaska.

Assistant Medical Director wanted for Mineral Springs Sanatorium, Cannon Falls, Minnesota, a 100-bed county tuberculosis hospital with active medical, surgical, out-patient, and investigative programs. Salary determined by experience. Furnished house and utilities supplied. Applicant must be male graduate of approved U. S. or Canadian medical school and eligible for Minnesota license. Address: E. V. Bridge, M.D., Superintendent.

Full-time staff physician wanted for the Idaho State Tuberculosis Hospital, Gooding, Idaho. New, fully modern hospital building nearing completion to replace several small, antiquated units, bringing the total bed capacity to 100-120 beds. Salary governed by training and experience. Apply: Medical Director, Idaho State Tuberculosis Hospital, Gooding, Idaho.

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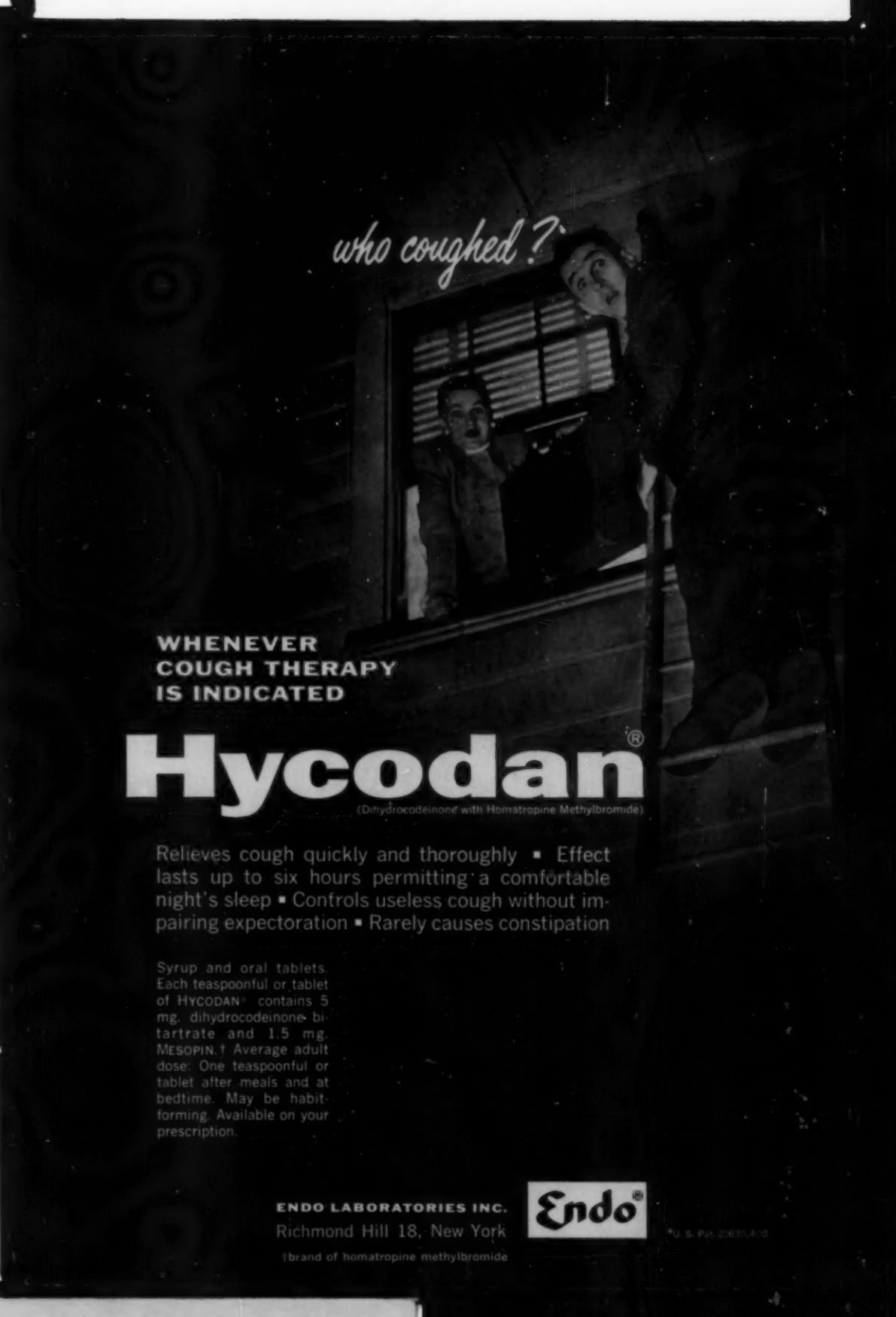
Gerald L. Crenshaw, M.D., Oakland
Glenroy N. Pierce, M.D., San Francisco
James Kieran, M.D., Oakland
Robert Stone, M.D., Oakland
William B. Leftwich, M.D., Oakland



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